NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Contents:

The following documents are made available to consultees and commentators:

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

Pre-technical engagement documents

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

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Leukaemia Care-Lymphoma Action-CLL Support Association
   b. UK CLL Forum-British Society for Haematology

4. **External Assessment Report** prepared by Aberdeen HTA Group

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Professor Nagesh Kalakonda – clinical expert, nominated by Janssen-Cilag Ltd
   b. Dr Nicolas Martinez-Calle – clinical expert, nominated by UK CLL Forum-British Society for Haematology
   c. Stephen Abrahams – patient expert, nominated by the CLL Support Association

8. **Technical engagement responses from stakeholders:**
   a. Leukaemia Care

9. **External Assessment Report critique of company response to technical engagement** prepared by Aberdeen HTA Group

Any information supplied to NICE which has been marked as confidential, has been

redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma [ID3860]

Document B

Company evidence submission

June 2022

File name	Version	Contains confidential information	Date
ID3860_Janssen_Ibrutinib_Document B_FINAL_[REDACTED] – Sept2022	September update	NO	21st June 2022

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AFT	Accelerated failure time
AIC	Akaike information criteria
ALC	Absolute lymphocyte count
AMR	Annual mortality rate
ANC	Absolute neutrophil count
ATC	Average treatment effect in the control population
ATO	Average treatment effect in the combined/overall population
ATT	Average treatment effect in the treated population
BCL-2	B-cell lymphoma-2
BCR	B-cell receptor
BIC	Bayesian information criteria
BM	Bone marrow
BNF	British National Formulary
BR	Bendamustine + rituximab
BSA	Body surface area
BSC	Best supportive care
BSH	British Society of Haematology
BTK	Bruton's tyrosine kinase
CD20	Cluster of differentiation 20
CDF	Cancer Drugs Fund
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CIT	Chemo-immunotherapy
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine clearance
CRi	Complete response with incomplete bone marrow recovery
CSR	Clinical study report
CT	Computerised tomography
CYP3A	Cytochrome P450, family 3, subfamily A
del11q	11q deletion
del17p	17p deletion
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	European Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency

Abbreviation	Definition
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-3L	EuroQoL-5 Dimension-3 Levels
EQ-5D-5L	EuroQoL-5 Dimension-5 Levels
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FC	Fludarabine + cyclophosphamide
FCR	Fludarabine + cyclophosphamide + rituximab
FD	Fixed duration
FISH	Fluorescent in situ hybridisation
FR	Fludarabine + rituximab
G-CSF	Granulocyte colony-stimulating factor
GPM	General population mortality
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSE	Health Survey for England
HTA	Health Technology Assessment
I+R	Ibrutinib + rituximab
I+V	Ibrutinib + venetoclax
ICER	Incremental cost-effectiveness ratio
IGHV	Immunoglobulin heavy chain variable region
INMB	Incremental net monetary benefit
INV	Investigator
IPD	Individual patient data
IPTW	Inverse probability for treatment weighting
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
iwCLL	International workshop on chronic lymphocytic leukaemia
KM	Kaplan-Meier
LDH	Lactic acid dehydrogenase
LDi	Largest diameter
LY	Life year
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRD	Minimal residual disease
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
Nodular PR	Nodular partial response
O-Clb	Obinutuzumab + chlorambucil
OR	Odds ratio

Abbreviation	Definition
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PB	Peripheral blood
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Progress after next line (second line) of treatment
PH	Proportional hazards
PICOS	Population, Intervention, Comparison, Outcome, Study design
PLD	Patient-level data
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
R/R	Relapsed/refractory
RCT	Randomised controlled trial
RMME	Repeated-measures linear mixed-effects
SD	Standard deviation
SE	Standard error
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TEM	Treatment-effect modifiers
TFI	Treatment-free interval
TLS	Tumour lysis syndrome
TP53	Tumour protein 53
TSD	Technical Support Document
TTF	Time to treatment failure
TTFR	Time to first response
TTNT	Time to next treatment
UK	United Kingdom
ULN	Upper limit of normal
uMRD	Undetectable minimal residual disease
US	United States
VAS	Visual analogue scale
VBA	Visual Basic for Applications
VenO	Venetoclax + obinutuzumab
VenR	Venetoclax + rituximab
VPLD	Virtual patient-level data
WTP	Willingness to pay

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

B.1.1 Decision problem

This single technology appraisal evaluates the clinical- and cost-effectiveness of fixed duration (FD) treatment with ibrutinib in combination with venetoclax (I+V) for patients with previously untreated chronic lymphocytic leukaemia (CLL). The anticipated marketing authorisation wording is: Ibrutinib in combination with venetoclax is indicated for the treatment of adult patients with previously untreated CLL.

This submission considers three populations, defined by either mutation status or suitability for intensive chemo-immunotherapy (CIT; fludarabine + cyclophosphamide + rituximab [FCR]) based on patient fitness, in line with the classification used in recent appraisals TA689 and TA663.(1, 2) There are no standard criteria for determining fitness level in CLL, but in routine clinical practice, the assessment of fitness includes factors such as age, presence and severity of comorbidities and performance status (PS).

The economic analysis follows the National Institute for Health and Care Excellence (NICE) reference case and therefore ensures alignment with the NICE decision problem.

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

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated CLL	As per final scope	NA
Intervention	I+V	As per final scope	NA
Comparator(s)	For people without del17p or TP53 mutation: • FCR • BR, for people for whom fludarabine-based therapy is unsuitable • O-Clb, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable • acalabrutinib, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable • VenO, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable For people with del17p or TP53 mutation: • acalabrutinib • VenO • ibrutinib alone, for people for whom CIT is unsuitable • idelalisib with rituximab	For people with no del17p mutation, for whom fludarabine-based therapy is suitable (i.e., FCR-suitable population): • FCR For people with no del17p mutation, for whom fludarabine-based therapy is unsuitable (i.e., FCR-unsuitable population): • O-Clb • VenO • acalabrutinib For people with del17p/TP53 mutation (i.e., high-risk population): • VenO • acalabrutinib • ibrutinib alone, for people for whom CIT is unsuitable	BR has been excluded as a relevant comparator for patients without a del17p/TP53 mutation, because it is rarely used in clinical practice and no longer recommended in the 2022 BSH guidelines.(3) This was validated at an advisory board of clinical and health economic experts conducted in March 2022(4) and was an assumption accepted by NICE in TA663.(1) Idelalisib with rituximab has been excluded as a relevant comparator for patients with a del17p/TP53 mutation because it is rarely used in clinical practice and clinical experts agree that it has now been superseded by ibrutinib and acalabrutinib due to the higher risk of infection and death. This was an approach accepted by NICE in the acalabrutinib (TA689) and VenO appraisals (TA663)(1, 2) and validated by clinical expert opinion in May 2022.(5)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • OS • PFS • response rates (including CR) • MRD • adverse effects of treatment • HRQoL	As per final scope	NA
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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 PSS perspective. The availability and cost of biosimilar and generic products should be considered. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered.	As per final scope and reference case	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people with del17p/TP53 mutation • according to IGHV mutation status (mutated or unmutated) • people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable	The submission addresses the following three populations: • people for whom fludarabine-based therapy is suitable • people for whom fludarabine-based therapy is unsuitable • people with del17p/TP53 mutation	IGHV test results are not required by NICE or CDF criteria to receive a specific treatment in first-line CLL and ibrutinib is efficacious independent of IGHV status;(6) therefore, the results in the FCR-suitable and FCR-unsuitable populations are more representative of UK clinical practice than in populations determined by IGHV mutation status. Patients from GLOW have co-morbidities which would make them unsuitable for treatment with FCR or BR – given that BR is not routinely used in clinical practice, a BR-unsuitable subgroup was not incorporated in the model. However, the results for the FCR-unsuitable population are generalisable to a BR-unsuitable population.
Special considerations including issues related to equity or equality	None	There is an urgent need for access to novel treatments for younger, fitter patients with CLL as currently only FCR or VenO via the CDF are available to them, with no access to a fully oral treatment. I+V will address this inequality.	

BR = bendamustine + rituximab; BSH = British Society of Haematology; CDF = Cancer Drugs Fund; CIT = chemo-immunotherapy; CLL = chronic lymphocytic leukaemia; CR = complete response; del17p = 17p deletion; FCR = Fludarabine + cyclophosphamide + rituximab; HRQoL = health-related quality of life; I+V = ibrutinib + venetoclax; IGHV = Immunoglobulin heavy chain variable region; MRD = minimal residual disease; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; O-Clb = obinutuzumab + chlorambucil; OS = overall survival; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; TA = technology appraisal; TP53 = tumour protein 53; UK = United Kingdom; VenO = venetoclax + obinutuzumab

B.1.2 Description of the technology being evaluated

A link to the latest European public assessment report (EPAR) for ibrutinib is provided in Appendix C. The summary of product characteristics (SmPC) for I+V is not yet available.

Table 2 Technology being evaluated

UK approved name and brand name	UK approved name: Ibrutinib Brand name: IMBRUVICA®
Mechanism of action	Ibrutinib and venetoclax have distinct and complementary mechanisms of action that are effective in inducing CLL cell death. • Ibrutinib is a potent, small-molecule inhibitor of BTK that forms a covalent bond with a cysteine residue in the BTK active site, leading to sustained inhibition of BTK. Inhibition of BTK disrupts BCR signalling and thereby reduces malignant B-cell proliferation and survival, cell migration and substrate adhesion.(7) • Venetoclax is a potent, selective inhibitor of BCL-2, an anti-apoptotic protein mediating tumour cell survival. Venetoclax has demonstrated cytotoxic activity towards tumour cells overexpressing BCL-2.(8) Ibrutinib mobilises CLL cells out of lymph nodes and lymphoid niches, removing them from the supportive lymphoid microenvironment that can aid the development of resistance to venetoclax.(9, 10) In the periphery (blood and BM), where venetoclax is more active, ibrutinib specifically enhances CLL cell dependence on BCL-2, resulting in increased sensitivity to venetoclax and accelerated cell apoptosis.(9, 11) Ibrutinib and venetoclax preferentially target distinct cell compartments and CLL sub-populations, effectively eliminating both dividing and resting CLL cells.(12)
Marketing authorisation/CE mark status	A marketing authorisation application for the indication of interest was submitted to the EMA in November 2021. The anticipated date of CHMP positive opinion is [redacted] and of EMA marketing authorisation approval for ibrutinib in this indication is [redacted]. A marketing authorisation application for the indication of interest is to be submitted to the MHRA using the [redacted] in [redacted]. MHRA marketing authorisation approval is expected in [redacted].
Indications and any restriction(s) as described in the SmPC	Ibrutinib currently has marketing authorisation from the EMA and MHRA in the following therapeutic indications related to CLL:(7, 13)

	• Ibrutinib as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. • Ibrutinib as a single agent or in combination with BR is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. The anticipated marketing authorisation in the UK is as follows: ibrutinib (IMBRUVICA®) in combination with venetoclax is indicated for the treatment of adult patients with previously untreated CLL.
Method of administration and dosage	Ibrutinib is administered orally; the dose is one 420 mg tablet once daily for 15 cycles (defined as 28 days). Ibrutinib is initially administered as monotherapy for the first three cycles, and in combination with venetoclax for 12 cycles. Venetoclax is administered orally; the dose starts with a 5-week ramp-up (1 week each of 20, 50, 100, 200 and 400 mg once daily), followed by 400 mg once daily thereafter from Cycle 4 to Cycle 15.
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	Confirmed list price of ibrutinib: • 28-tab pack (420 mg) = £4,292.40 Confirmed list price of venetoclax: • 14-tab pack (10 mg) = £59.87 (1 week, 20 mg per day) • 7-tab pack (50 mg) = £149.67 (1 week, 50 mg per day) • 7-tab pack (100 mg) = £299.34 (1 week, 100 mg per day) • 14-tab pack (100 mg) = £598.68 (1 week, 200 mg per day) • 112-tab pack (100 mg) = £4,789.47 (Cycle 5 until end of Cycle 15, 400 mg per day [28 days pack]) At list price, the total cost of the FD I+V regimen (15 cycles of ibrutinib and 12 cycles of venetoclax, including the ramp-up) is £118,177.73
PAS	Currently a simple discount PAS is in place for all ibrutinib indications funding via baseline commissioning. This existing discount of [redacted]% will apply to the indication covered by this submission making the price of a 28-tab pack of ibrutinib [redacted]. AbbVie has a commercial arrangement for venetoclax. This makes venetoclax available to the NHS with a discount. The size of the discount is commercial in confidence.

BCL-2 = B-cell lymphoma-2; BCR = B-cell receptor; BM = bone marrow; BR = bendamustine + rituximab; BTK = Bruton's tyrosine kinase; CHMP = Committee for Medicinal Products for Human Use; CLL = chronic lymphocytic leukaemia; EMA = European Medicines Agency; FD = fixed duration; I+V = ibrutinib + venetoclax; MHRA = Medicines and Healthcare products Regulatory Agency; NHS = National Health Service; PAS = patient access scheme; SmPC = summary of product characteristics; UK = United Kingdom

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

Disease overview and burden

- CLL is a type of blood cancer, which is relatively rare (around 1% of new cancers are CLL) and is typically diagnosed in older people (median age at diagnosis of 72 years in the United Kingdom [UK]).(14, 15)
- The clinical manifestations of CLL can have a substantial negative impact on patients' quality of life (QoL) as a result of disease-related symptoms (such as fatigue, recurrent infections and anaemia); treatment-related adverse events (AEs); and the psychological, socioeconomic and functional effects of living with the disease.(16, 17)
- Patients with CLL have been shown to have significantly lower emotional well-being than the general population and patients with other types of cancer.(16) CLL also imposes a considerable economic burden on patients, their families, the healthcare system and society.(17-19)

Clinical pathway of care

- Treatment decisions are influenced by age, fitness and mutation status.(3, 20, 21) The BSH guidelines recommend screening for TP53 disruption (i.e., del17p and/or TP53 mutation) before initiating treatment since patients with these genetic mutations are considered a high-risk group.(3)
  - In patients with del17p/TP53 mutations (high-risk patients), the options include idelalisib + rituximab (idelalisib is oral but treat to progression and rituximab is FD, given via intravenous [IV] infusion), venetoclax + obinutuzumab (VenO; FD but includes IV obinutuzumab infusions), acalabrutinib (oral but treat-to-progression) or ibrutinib (oral but treat to progression).
  - In patients without del17p/TP53 mutations for whom FCR/ bendamustine + rituximab (BR) is suitable, the only treatment options have been CIT (FCR/BR) for decades, with the recent addition of VenO (only through the Cancer Drugs Fund [CDF]).
  - In patients without del17p/TP53 mutations for whom FCR/BR is unsuitable, the options include obinutuzumab + chlorambucil (O-Clb; a CIT), VenO (FD but includes IV obinutuzumab infusions) or acalabrutinib (oral but treat to progression).

Unmet need

- Despite the addition of new therapies and subsequent updates to treatment guidelines for CLL management over the last decade,(3, 22) currently, patients with previously untreated CLL lack a convenient all-oral once daily FD, chemotherapy-free regimen that can be taken at home (without the need for infusion-based hospital treatments).
- This unmet need includes patients' desire for more effective disease management, including treatments with fewer side effects and which do not contribute to the 'medicalisation' of patients' lives (process by which patients become increasingly defined by their disease [and its treatment]). I+V would address these unmet needs.

Proposed positioning of I+V

- It is anticipated that I+V will be used as first-line treatment in patients considered suitable for FCR (in line with the phase II CAPTIVATE study population) and unsuitable for FCR (in line with the phase III GLOW study population), as well as in high-risk patients.

B.1.3.1 Disease overview

CLL is the most common type of leukaemia(23) and is a lymphoproliferative B-cell malignancy characterised by the progressive expansion of monoclonal B lymphocytes in the blood, bone marrow (BM), lymph nodes or other lymphoid tissue.(24, 25) CLL is generally an incurable disease and is life-threatening due to the development of immune cytopenias and impaired production of normal immunoglobulin.(20, 26, 27)

Small lymphocytic lymphoma (SLL) is a leukaemic lymphocytic lymphoma that is considered to be the same entity as CLL by the World Health Organisation and will be referred to as CLL from here on.(25, 28)

Clinical presentation, staging and diagnosis

Guidelines from the 2018 International Workshop on CLL (iwCLL) specify that a diagnosis of CLL requires the presence of ≥5 x 10^9/L B lymphocytes in the peripheral blood (PB) for at least 3 months.(25) These diagnostic criteria are similar to criteria published in 2012 by the British Society of Haematology (BSH), in 2021 by the European Society for Medical Oncology (ESMO) and in 2022 by the US National Comprehensive Cancer Network (NCCN).(20, 21, 29)

The majority of patients with CLL (74%) have no symptoms at the time of diagnosis and are only diagnosed when a routine blood count uncovers an absolute lymphocytosis.(24, 29-31) In patients who are symptomatic at diagnosis, there are a wide range of presenting features and physical and laboratory abnormalities.(24, 29) Common clinical signs may include enlarged lymph nodes, liver, spleen or bruising and patients may display typical cancer related symptoms such as fever, chills, night sweats and weight loss. Once a patient is diagnosed, clinical staging of CLL is established based on a physical examination and complete blood counts.

Clinical staging systems used in CLL include the Binet system, which is mostly used in the UK and Europe, and the Rai classification system, which is mostly used in North America.(32, 33) The Binet System classifies patients in three stages as A, B or C, based on the number of red blood cells and platelets and the number of areas of the lymphatic system that are enlarged.(33) The Rai system classifies patients in five

stages as 0, I, II, III or IV, based on the number of lymphocytes, red blood cells and platelets and whether the lymph nodes, spleen or liver are enlarged.(32) The Binet C and Rai III/IV represent patients with advanced disease and at high risk, respectively.(20)

The prognosis of patients with CLL is dependent on a variety of patient-related (age, gender, comorbidities and PS), disease-related (disease stage, cytogenetics, marrow failure, immunodeficiency, lymphomatous transformation and biomarkers) and treatment-related (type of treatment, response, toxicity and minimal residual disease [MRD] status) factors.(29) In particular, TP53 aberration (del17p and/or TP53 mutation) is an established prognostic marker in CLL, providing the strongest prognostic and predictive relevance among the relevant cytogenetic factors in CLL; del17p and/or TP53 mutation predict an aggressive disease course and are associated with a poor prognosis and a negative impact on treatment outcomes.(20)

Epidemiology

CLL accounts for 1% of total cancer cases in the UK with around 3,800 new cases in the UK every year, corresponding to 10 cases each day (based on 2016-2018 data from Cancer Research UK).(14) There were 3,157 new cases of CLL in England in 2017 based on data from the Office for National Statistics.(34) CLL meets the UK Medicines and Healthcare products Regulatory Agency (MHRA) criteria for a rare disease (prevalence of <5 per 10,000),(35, 36) with a prevalence of ~3 per 10,000 people,(14) based on a population of 62.8 million in 2010.(37) Table 3 presents the age-standardised incidence rates.

Table 3 CLL incidence rates in England and Wales (2016-2018)

	England	**Wales**	**UK**
Age-standardised incidence rates	6.5 per 100,000 people	4.8 per 100,000 people	6.2 per 100,000 people

CLL = chronic lymphocytic leukaemia
Source: Cancer Research UK, 2021(14)

CLL is typically diagnosed between the ages of 65 and 74 years, with a median age at diagnosis of 72 years reported in England; 27% of patients with CLL are diagnosed

below 65 years.(15) CLL is a chronic disease with patients experiencing episodes of relapse and remission, although the natural course of CLL is highly variable.(22) In the UK, the age-standardised mortality rate is 1.5 per 100,000; since the early 1970s, mortality rates for CLL have decreased in most age groups, excluding in ≥80 year olds (28% increase).(38) Survival decreases with advancing age (Table 4).

Table 4 5-year survival rates for patients with CLL in the UK, by age range (2006-2010)

Age range	5-year survival rates
55 and 64 years of age	82%
65 and 74 years	71%
75 and 84 years of age	56%
≥85 years	30%

CLL = chronic lymphocytic leukaemia; UK = United Kingdom
Source: Pulte, 2015(15)

B.1.3.2 Disease burden

CLL is a chronic disease which impacts patients' QoL negatively through the symptoms experienced, treatment-related AEs, impact on work and family life. Additionally, there is an economic burden associated with CLL.

Symptom burden

CLL develops slowly and most patients are asymptomatic at the time of diagnosis. Non-specific symptoms of CLL include weight loss, fatigue, night sweats and fever.(24, 29, 39) Symptoms of CLL can include swollen lymph nodes, having frequent infections, severe sweating at night, weight loss, breathlessness and tiredness due to anaemia.

CLL patients have an increased risk of other secondary cancers and infections, because CLL is a cancer of B-lymphocytes and consequently causes impairment to the immune system through impact of the disease on the lymphatic system, spleen and other organs.(40, 41) During an advisory board with patients, they identified risk of infection, along with fatigue, as a key factor that limited their social activities, which further impacts their QoL.(42)

Fatigue is one of the most common symptoms of CLL, and the severity of fatigue is higher in patients with CLL compared to the general population and increases in line with disease stage.(16, 43, 44) CLL trustees/patients who participated in an advisory board in 2022 said “I hadn’t experienced fatigue like this” and another person with CLL said “the fatigue meant I wasn’t pleasant to be around, so I felt frustrated and guilty”.(18)

In addition to the symptom burden of CLL, AEs associated with treatment add to the clinical burden of CLL.(45) The most commonly reported AEs among patients receiving FCR were anaemia, neutropenia (leading to infections) and leukocytosis (resulting in fever, bruising, fatigue).(18)

Impact on quality of life

In the UK, many patients with CLL are on ‘Watch and Wait’, which is a process whereby patients with CLL are regularly monitored to track disease progression, with treatment only initiated once intervention criteria are met and treatment required.(20) This ‘Watch and Wait’ strategy is supported by studies that failed to demonstrate a survival advantage with early intervention with chemotherapy.(20) It has been estimated that the proportion of symptomatic (eligible to receive treatment at initial diagnosis) and asymptomatic (‘Watch and Wait’) patients ranges from 26% to 34% and 66% to 74%, respectively.(30) During the ‘Watch and Wait’ period, patients are frequently monitored and face constant uncertainty and emotional strain.

CLL trustees/patients who participated in an advisory board in 2022 described ‘Watch and Wait’ as “lonely and worrying” and “found the thought of waiting to be ill very anxiety-inducing”. They also mentioned that “the diagnosis can come as a shock, especially for those who are younger” given that patients are mostly asymptomatic. They said that ‘Watch and Wait’ made them “apprehensive about the future and worried about potential impacts of the disease and treatment, not knowing when it will come”.(18)

The clinical manifestations of CLL can have a substantial negative impact on patients’ QoL as a result of disease-related symptoms (such as fatigue, recurrent infections and

anaemia); treatment-related AEs; and the psychological, socioeconomic and functional effects of living with the disease.(16, 17)

The emotional well-being of patients with CLL has been shown to be significantly lower than that of the general population (p=0.001), as well as that of patients with other types of cancer (p=0.001).(16) In addition, compared with the general population, patients with CLL experience worse depression, fatigue, anxiety, sleep disturbance and detriment in physical functioning, social functioning and pain interference.(17)

The effect of CLL treatment on QoL was evaluated in a UK study which recruited 100 individuals from the general population to rate nine different health states within the typical disease and treatment course of CLL.(42) The CLL health state of “progression-free survival (PFS) without therapy” was considered the least burdensome, followed by “PFS without second-line therapy” and “PFS on initial therapy oral treatment” (mean utility scores: 0.82, 0.71 and 0.71, respectively).(42) This study highlights the importance of convenient therapies and long-lasting PFS when considering QoL in patients with CLL.(42) Currently in the first-line setting, patients with CLL lack a convenient all-oral once daily FD treatment which can be taken at home.

Economic burden

CLL also imposes a considerable economic burden on patients and their families, as well as on the healthcare system and society. Hospitalisation is a primary cost driver for patients with CLL in the UK, with outpatient and hospice care adding to overall healthcare costs incurred by patients initiating first-line treatment.(19) The economic burden of CLL increases further when patients relapse (especially when disease progression occurs early), with increased healthcare resource use (including inpatient admissions and outpatient visits) driving cost increases.(17, 46-48)

Additional burden on patients stems from the impact of CLL on their ability of work. Once diagnosed with CLL, patients may need sick leave and/or a reduction in work hours, and maybe even stopping work eventually. A CLL trustee/patient who participated in an advisory board in 2022 said “I felt so tired all the time – all my energy

was going into work. I had to have some energy for my family, so I stopped working". This leads to an impact on their personal finances, causing an emotional burden.(18)

B.1.3.3 Clinical pathway of care

Certain patients with CLL may be considered for allogeneic stem cell transplantation (patients refractory to CIT with TP53 mutation or del17p, but fully responsive to novel inhibitor therapy; patients refractory to CIT and to novel inhibitor therapy; patients with Richter's transformation in remission after therapy and clonally related to CLL).(20) Otherwise, CLL remains an incurable disease for symptomatic patients who require treatment but are ineligible for haematopoietic stem cell transplantation.(20) The clinical burden of CLL is high, particularly as it is a chronic relapsing and remitting disease.(49) Historically, the choice of therapy was a trade-off between efficacy and tolerability, especially for CIT, and often depended on the patient's ability to tolerate treatment.(49) However, the role of CIT in first-line treatment has diminished following the approval of targeted pathway inhibitors in recent years.(3)

Treatment decisions are influenced by age, fitness and mutation status.(3, 20, 21) Agreement on a definition for fitness status has not been reached, but the following thresholds are commonly cited:(21, 50)

- More fit: CIRS ≤6, CrCl ≥70 mL/min and ECOG PS <2
- Less fit: CIRS >6 and CrCl <70 mL/min

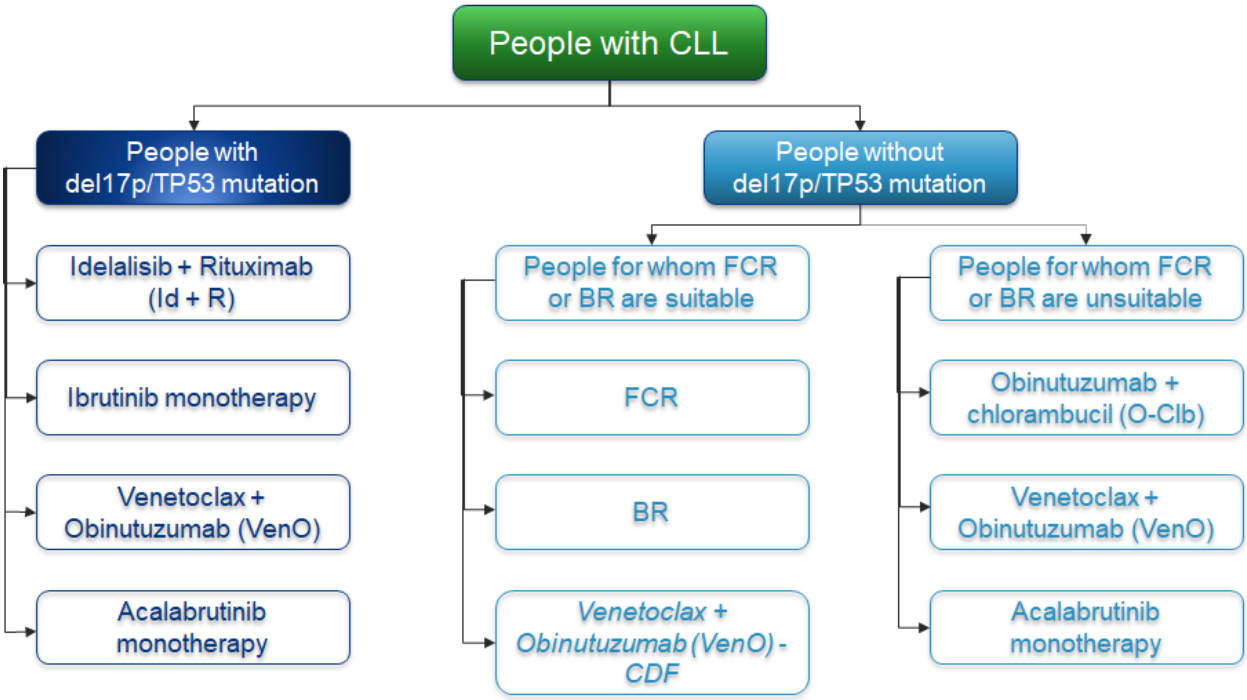
The BSH guidelines recommend screening for TP53 disruption (i.e., del17p and/or TP53 mutation) before initiating treatment since patients with these genetic mutations are considered a high-risk group.(3) The presence of del17p/TP53 mutation remains a statistically significant negative prognostic factor regardless of patient's fitness when treated with CIT, such as O-Clb and FCR, as well as other CLL treatments, such as VenO.(20, 51-53)

Despite the addition of new therapies and subsequent updates to treatment guidelines for CLL management over the last decade,(3, 22) currently, patients with previously

untreated CLL lack a convenient all-oral once daily FD, chemotherapy-free regimen that can be taken at home (without the need for infusion-based hospital treatments).

The current UK clinical pathway for first-line treatment of CLL is directed by NICE guidance, summarised in Figure 1. Current treatments which are recommended by NICE for previously untreated CLL are summarised in Table 5.

Figure 1 NICE-recommended clinical pathway for previously untreated CLL



BR = bendamustine + rituximab; CLL = chronic lymphocytic leukaemia; del17p = 17p deletion; FCR = fludarabine + cyclophosphamide + rituximab; TP53 = tumour protein 53

Table 5 Treatments recommended by NICE for previously untreated CLL

Treatment	Conditions of use per NICE	Regimen	Other Considerations
People without a del17p or TP53 mutation			
FCR (TA174)(54)	People for whom fludarabine in combination with cyclophosphamide is considered appropriate	FD regimen with rituximab (IV) and fludarabine and cyclophosphamide (both IV or oral administration)(54, 55)	• The long-term risk of infections and secondary neoplasms, leukaemias and myelodysplastic syndromes with CIT should be considered(20) • The risk of toxicity from intensive treatment is increased among patients aged >65 years old(49)
Bendamustine (TA216)(56)	People for whom fludarabine combination chemotherapy is not appropriate	FD regimen with bendamustine (IV), commonly in combination with rituximab (IV)(56, 57)	• BR is rarely used in clinical practice and is no longer recommended in the 2022 BSH guidelines.(1, 3)
O-Clb (TA343)(58)	People for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable	FD regimen with chlorambucil (oral) and obinutuzumab (IV)(59, 60)	• Administration of obinutuzumab should be performed under supervision by an experienced physician and in the presence of resuscitation facilities(59) • Premedication to reduce the risk of infusion-related reactions is required prior to the first cycle of obinutuzumab(59) • Other safety warnings include TLS, neutropenia, thrombocytopenia, worsening of pre-existing cardiac conditions, infections, hepatitis B virus reactivation and progressive multifocal leukoencephalopathy(59)

Treatment	Conditions of use per NICE	Regimen	Other Considerations
Acalabrutinib (TA689)(2)	People for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable	Continuous regimen with acalabrutinib (oral) administered until disease progression or unacceptable toxicity(61)	• Concomitant use of acalabrutinib with strong CYP3A inhibitors/inducers and proton pump inhibitors should be avoided(61) • Major haemorrhagic events (some with fatal outcome), serious infections (including fatal events), hepatitis B reactivation, grade 3 or 4 cytopenias, second primary malignancies and atrial fibrillation/flutter have been reported with acalabrutinib and are listed as special warnings in the SmPC(61)
VenO (TA663)(1)	People for whom fludarabine-based therapy or bendamustine-based therapy is unsuitable	FD regimen with venetoclax (oral) and obinutuzumab (IV)(8, 59)	• Both venetoclax and obinutuzumab are associated with a risk of TLS, requiring prophylaxis and monitoring during initial treatment plus dose titration for venetoclax(8, 59) • Other safety warnings with venetoclax include neutropenia, infections and coadministration with CYP3A4 inducers(8)
VenO (TA663 – CDF)(1)	People for whom fludarabine-based therapy or bendamustine-based therapy is suitable	See VenO row above	• Only available through CDF
People with a del17p or TP53 mutation (high-risk)			
Idelalisib with rituximab (TA359)(62)	People with a del17p or TP53 mutation	Continuous regimen with idelalisib (oral) administered until disease progression or unacceptable toxicity and rituximab (IV) administered for a FD(63)	• Idelalisib with rituximab is rarely used in clinical practice because it has an intensive dosing regimen and is associated with an increased infection risk(1, 2, 63)
Acalabrutinib (TA689)(2)	People with a del17p or TP53 mutation	See acalabrutinib row above	• See acalabrutinib row above

Treatment	Conditions of use per NICE	Regimen	Other Considerations
VenO (TA663)(1)	People with a del17p or TP53 mutation	See VenO row above	• See VenO row above
Ibrutinib (TA429)(64)	People who are high-risk (del17p/TP53 mutation) or in patients for whom CIT is unsuitable	Continuous regimen with ibrutinib (oral) administered until disease progression or unacceptable toxicity(7)	• Use of preparations containing St. John's Wort is contraindicated in patients treated with ibrutinib(7) • Concomitant use of ibrutinib with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers should be avoided whenever possible(7)

BR = bendamustine + rituximab; BSH = British Society for Haematology; CDF = Cancer Drugs Fund; CIT = chemo-immunotherapy; CLL = chronic lymphocytic leukaemia; CYP3A = cytochrome P450; del17p = 17p deletion; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; IV = intravenous; NICE = National Institute for Health and Care Excellence; O-Clb = obinutuzumab + chlorambucil; SmPC = summary of product characteristics; TLS = tumour lysis syndrome; TP53 = tumour protein 53; VenO = venetoclax + obinutuzumab

Recommendations from the BSH and recognised international and national authorities (ESMO and NCCN) also guide the UK clinical pathway. BSH, ESMO and NCCN treatment recommendations for previously untreated CLL, stratified by fitness and mutation status, are summarised in Table 6.

Table 6 Treatment guidelines for previously untreated CLL

Patient category	BSH 2022[a](3)	ESMO 2021(20)	NCCN 2022[c] (preferred options only, in alphabetical order)(21)

Fit patients without TP53 disruption (del17p or TP53 mutation)	• Preferred: VenO via the CDF, acalabrutinib + obinutuzumab,[a] ibrutinib[a]
	• Alternative: FCR for patients with mutated IGHV
		• IGHV unmutated
		  ○ Preferred: Ibrutinib
		  ○ Alternative: CIT (FCR or BR[b])
		• IGHV mutated and without del17p
		  ○ Preferred: CIT (FCR or BR[b]) or ibrutinib
			• Acalabrutinib ± obinutuzumab, ibrutinib, VenO, or zanubrutinib

Unfit patients without TP53 disruption (del17p or TP53 mutation)	• VenO, acalabrutinib ± obinutuzumab,[a] ibrutinib[a]	• IGHV unmutated
		  ○ Preferred: VenO, ibrutinib or acalabrutinib
		  ○ Alternative: CIT (O-Clb)
		• IGHV mutated
		  ○ Preferred: VenO, CIT (O-Clb), ibrutinib or acalabrutinib
			• Acalabrutinib ± obinutuzumab, ibrutinib, VenO, or zanubrutinib

Patients with TP53 disruption (del17p or TP53 mutation)	• Fit
	  ○ Preferred: Acalabrutinib ± obinutuzumab,[a] ibrutinib
	  ○ Alternative: Venetoclax monotherapy in patients with a contraindication to BCR inhibitors, or VenO
	• Unfit
	  ○ VenO, acalabrutinib ± obinutuzumab,[a] ibrutinib[a]
		• Preferred: Ibrutinib, acalabrutinib, VenO, venetoclax or idelalisib + rituximab	• Acalabrutinib ± obinutuzumab, ibrutinib, VenO, or zanubrutinib

BCR = B-cell receptor; BR = bendamustine + rituximab; BSH = British Society for Haematology; CD20 = cluster of differentiation 20; CDF = Cancer Drugs Fund; CIT = chemo-immunotherapy; CLL = chronic lymphocytic leukaemia; CrCl = creatinine clearance; del17p = 17p deletion; ESMO = European Society for Medical Oncology; FCR = fludarabine + cyclophosphamide + rituximab; IGHV = immunoglobulin heavy chain variable region; IV = intravenous; NCCN = National Comprehensive Cancer Network; O-Clb = obinutuzumab + chlorambucil; TP53 = tumour protein 53; VenO = venetoclax + obinutuzumab

[a] The BSH guidelines include all licensed treatments; however, note that the following are not reimbursed in the UK in the first-line setting: ibrutinib monotherapy for patients without del17p/TP53 mutation and acalabrutinib + obinutuzumab

[b] Use of BR can be considered for patients aged >65 years
[c] Fit patients were defined as those aged <65 years and without significant comorbidities; unfit patients were defined as those aged ≥65 years or younger patients with significant comorbidities (CrCl <70 mL/min)

B.1.3.4 Unmet need

Based on the information presented above, the current treatment options used in UK clinical practice (and the relevant comparators for the three populations considered in this submission) are summarised in Table 7.

Table 7 Summary of first-line treatment options for CLL

Regimen	Treatment duration	Route of administration
FCR-suitable patients		
FCR	FD	IV (rituximab) and oral or IV (fludarabine and cyclophosphamide)
FCR-unsuitable patients		
O-Clb	FD	IV (obinutuzumab) and oral (chlorambucil)
VenO	FD	IV (obinutuzumab) and oral (venetoclax)
Acalabrutinib	Continuous	Oral
High-risk patients		
Acalabrutinib	Continuous	Oral
VenO	FD	IV (obinutuzumab) and oral (venetoclax)
Ibrutinib	Continuous	Oral

BR = bendamustine + rituximab; CLL = chronic lymphocytic leukaemia; del17p = 17p deletion; FCR = fludarabine + cyclophosphamide + rituximab; IV = intravenous; O-Clb = obinutuzumab + chlorambucil; TP53 = tumour protein 53; VenO = venetoclax + obinutuzumab

Unmet need from a patient perspective

Treatment choice is informed by physicians recommending the most appropriate treatment, based on fitness and mutation status, and patient choice. There is a strong patient preference for less toxic therapies, without loss of efficacy, which can reduce the burden of hospital appointments.

Oral treatments

CLL trustees/patients who participated in an advisory board in 2022 highlighted the following:(18)

- “An oral therapy has got to win hands down compared to a combination or infusion therapy. The disruption, logistics, the discomfort - all of that”
- “An oral thing would be great, really handy. Be in contact less often with doctors is a good thing”
- “If you physically don’t have to go to the hospital, it’s just easier”

- “I don’t know who would choose an infusion if you could take a pill”
- “There is a lot more freedom if you are just taking the pills. You could go on vacation”
- “So much better for the quality of life to take pills at home”

Fixed duration treatments

CLL trustees/patients who participated in an advisory board in 2022 highlighted the following:(18)

- “The fixed thing is fantastic. You only have to have it for a certain time and then you're done. The fixed is good for me.”
- “I will have a time when I don't have to take any drugs. And that has to be a good thing”
- “You can live normally and plan things”
- “I think I would like the short duration. Done and dusted.”

Currently, patients with previously untreated CLL lack a convenient all-oral once daily, FD, chemotherapy-free treatment regimen that can be taken at home (without the need for infusion-based hospital treatments) and that can be administered regardless of patient fitness and mutation status. An oral therapy would give patients the convenience, freedom and independence associated with treatment administered at home.

Treatment with an all-oral regimen would also reduce the number of hospital visits needed. Hospital visits can increase anxiety levels in anticipation of the appointments. A positive recommendation for I+V would reduce the need for: elderly or frail patients with mobility issues to rely on others for transport to a hospital; young and fit patients in the workforce to repeatedly request time off work; and parents with young children to organise childcare during hospital appointments. CLL trustees/patients who participated in an advisory board in 2022 highlighted “it’s inconvenient to go to hospital, to drive there and pay for parking”, described hospital appointments as “disruptive,

uncomfortable and having to organise logistics” and mentioned “not having those trips to the hospital is just easier on the mind. People start to get anxious the week before they go into hospital and then really nervous on the day, and they're just sweating by the time they get in there, even if it's just a check-up”.(18)

A FD regimen would reduce the duration of patient exposure to treatment compared to treat to progression comparators, decrease the duration of AEs and allow patients to have a ‘treatment holiday’ between finishing first-line treatment and initiating second-line treatment after disease progression.

CLL trustees/patients who participated in an advisory board in 2022 highlighted wanting to regain “some sort of control” and live “as normal a life as possible” as key aspects of the impact of CLL treatment on daily life and emotional well-being.(18)

Additionally, clinicians would value the option to administer a combination of effective agents upfront to reduce the resource burden associated with relapse.(17, 46-48) This would have positive resource implications for the National Health Service (NHS), which is currently recovering from a global pandemic, by helping to alleviate the backlog of patients waiting to be treated.

I+V will address these unmet needs, and help patients avoid a life of medicalisation (process by which patients become increasingly defined by their disease [and its treatment]) by reducing hospital appointments and offering patients a ‘treatment-free holiday’.

FCR-suitable patients

FCR-suitable patients with previously untreated CLL in the UK only had FCR as a treatment option for decades, with VenO becoming available in 2020 only through the CDF); no fully oral regimens are available to these patients.(3)

Toxicity and risks of secondary malignancy remain areas of concern with FCR.(3, 20) Patients being considered for FCR are typically younger people whose daily lives can be particularly impacted by the burden of hospital appointments for IV treatment

administration. These patients would thus greatly benefit from an all-oral treatment regimen conveniently administered at home, with reduced burden in terms of travel time to the hospital, time off work and childcare planning. A CLL trustee/patient who participated in an advisory board in 2022 mentioned she was told she would receive FCR because she was young and “could hit the disease hard” but she was “dreading FCR” because of the side effects.

FCR-unsuitable patients

FCR-unsuitable patients with CLL require convenient, all oral, FD treatment options that reduce burden on patients and carers. NICE-recommended treatment options for these patients are limited to FD regimens involving IV administration and the need for premedication (O-Clb and VenO) or an oral regimen that is administered continuously until disease progression (acalabrutinib). There remains an unmet need in this population for a treatment regimen that could be taken from home (leading to fewer hospital appointments), avoid the need for IV administration (especially beneficial in elderly and frail patients) and allow for a ‘treatment holiday’ after completion of the FD regimen.

High-risk patients

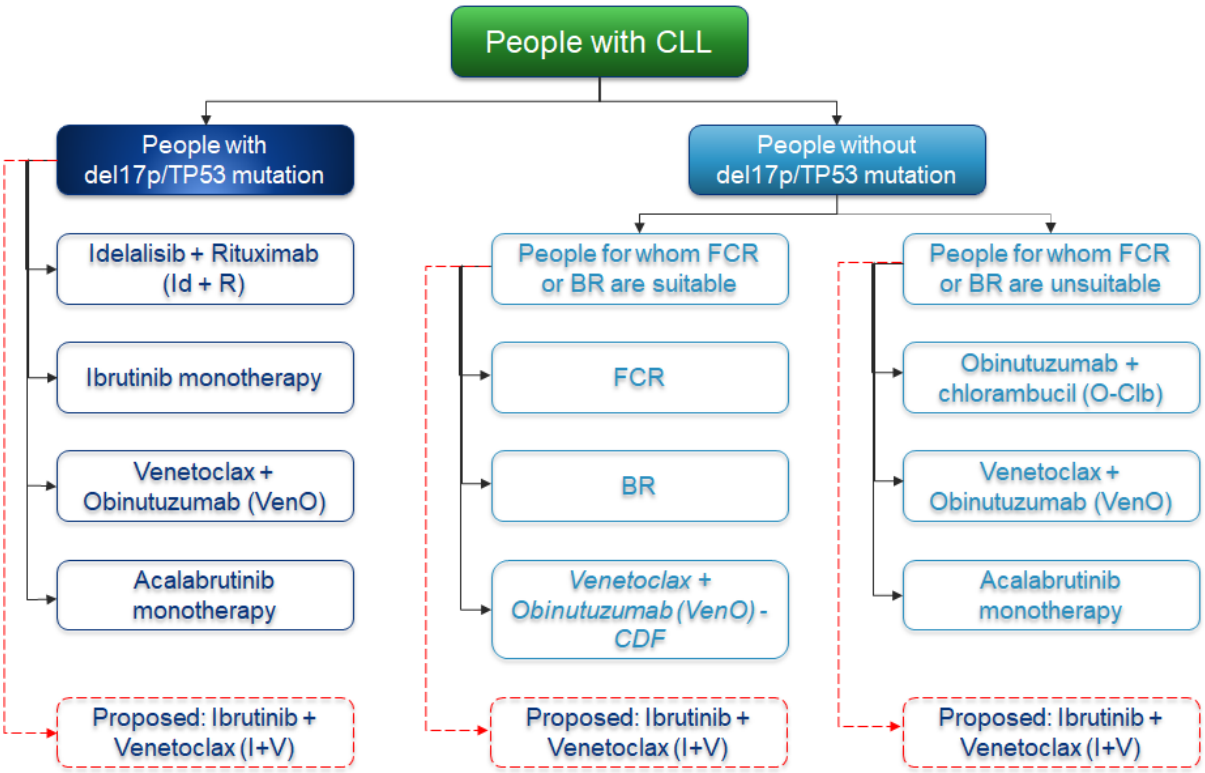
High-risk patients with previously untreated CLL face a poor prognosis, with del17p shown to have the worst prognosis among genetic mutations identified as important independent predictors of disease progression and survival in CLL.(65) An additional efficacious treatment option providing deep and durable responses would be valuable for these patients with high-risk disease. Furthermore, high-risk patients would benefit from an all oral, FD alternative to the currently available NICE-recommended therapies (acalabrutinib monotherapy, VenO and ibrutinib monotherapy).

B.1.3.5 Proposed positioning of I+V

The proposed positioning of I+V (an oral, once daily FD regimen) in the treatment pathway for previously untreated CLL is depicted in Figure 2. It is anticipated that I+V will be used as first-line treatment in patients considered suitable for FCR (in line with

the phase II CAPTIVATE study population) and unsuitable for FCR (in line with the phase III GLOW study population), as well as in high-risk patients.

Figure 2 Clinical pathway of care for previously untreated CLL, with proposed position of I+V in red



BR = bendamustine + rituximab; CLL = chronic lymphocytic leukaemia; del17p = 17p deletion; FCR = fludarabine + cyclophosphamide + rituximab; TP53 = tumour protein 53

B.1.4 Equality considerations

There is an urgent need for access to novel treatments for younger, fitter patients with CLL, as currently only FCR or VenO via CDF are available to them, both of which require IV infusions. I+V will address this inequality.

In addition to the clinical benefits, there is a social value judgement relating to reducing medicalisation which I+V is well positioned to address. Specifically, I+V helps patients avoid a life of medicalisation by reducing hospital appointments and offering patients a 'treatment-free holiday'.

A CLL trustee/patient who participated in an advisory board in 2022 highlighted the ‘medicalised’ feeling patients live with “You hear things like cancer is not going to define me, it does control you there's no doubt about it, you might think you have a certain control, but you do whatever the disease demands of you, so in that sense you are not in control.”(18)

B.2 Clinical effectiveness

A systematic literature review (SLR) identified two high-quality clinical trials for I+V in the relevant patient population as defined by the NICE scope (CAPTIVATE FD cohort and GLOW).

- CAPTIVATE was a non-comparative phase II trial designed to evaluate I+V in the FCR-suitable population in two cohorts (the FD cohort and the MRD cohort); the open-label, one-group FD cohort is in line with how I+V will be administered in clinical practice and is therefore of interest to this submission. The FD cohort was designed to evaluate the depth of response per complete response (CR)/CR with incomplete BM recovery (CRi; primary endpoint) following FD I+V.(66)
- GLOW was a randomised, open-label, multi-centre phase III trial designed to evaluate FD I+V vs. O-Clb among patients in the FCR-unsuitable population. The primary endpoint of GLOW was Independent Review Committee (IRC)-assessed PFS.(67)
- The extended follow-up analysis of both trials (median follow-up of 38.7 months in CAPTIVATE(68, 69) and 34.1 months in GLOW(67, 70)) informed the indirect treatment comparisons (ITCs) and economic analysis.

GLOW and CAPTIVATE demonstrated the efficacy of FD I+V in previously untreated CLL.

- In FCR-suitable patients in the CAPTIVATE FD cohort, INV-assessed CR/CRi rate (primary endpoint) was 55.9% (95% confidence interval [CI]: 47.5, 64.2) for patients without del17p at the primary analysis (median 27.9 months follow-up).(66) CR/CRi rates increased slightly to 58.1% (95% CI: 49.8, 66.4) with approximately 9 months of further follow-up.(68)
- Secondary endpoint analyses from CAPTIVATE FD cohort supported the favourable CR rates, with the majority of CRs being durable for at least 12 months.(66, 68)
- In FCR-unsuitable patients in GLOW, primary analysis (median follow-up of 27.7 months) concluded that patients treated with I+V had a significantly reduced risk of disease progression or death of 78% per IRC assessment (hazard ratio [HR] 0.22; 95% CI: 0.13, 0.36; nominal p<0.0001) compared to patients treated with O-Clb.(67) INV-assessed PFS was consistent with IRC-assessed PFS. PFS benefit with I+V vs. O-Clb was maintained long-term with approximately 6 months of further follow-up.(67, 70)
- Secondary endpoint analyses from GLOW indicated that the I+V group also had a significantly higher overall MRD negative rate in BM by NGS and significantly higher IRC-assessed CR/CRi compared to the O-Clb group at the primary analysis; the [redacted] and MRD negative rates with I+V remained high and the benefit vs. O-Clb was sustained throughout the first year after treatment completion.(70, 71) [redacted](70)

The safety profile of I+V is consistent with data about safety of use of ibrutinib and venetoclax in CLL.

- Together, results of CAPTIVATE and GLOW demonstrated an acceptable safety profile in patients with previously untreated CLL.(66, 67)
- With a 3-cycle lead-in, ibrutinib allowed for an initial reduction in tumour burden, decreasing the number of patients at higher risk of tumour lysis syndrome (TLS).(66, 67)

There are currently no data on direct comparisons of I+V with FCR, VenO or acalabrutinib, so ITCs were needed to derive comparative efficacy.

- In a patient-level data (PLD) ITC of I+V and FCR in the FCR-suitable population, I+V demonstrated statistically significant PFS advantage over FCR in patients without del17p with no missing covariate values. After adjustment using average treatment effect in the treated population (ATT) in the same population, a trend for better PFS with I+V over FCR was observed.
- Results of an anchored matching-adjusted indirect comparison (MAIC) show that the HRs for PFS and OS were in favour of I+V vs. VenO, before and after adjusting for baseline characteristics. HRs for PFS and OS from another anchored MAIC were in favour of acalabrutinib before adjusting, but not statistically significant. After adjusting for baseline characteristics, PFS and OS outcomes were similar between I+V and acalabrutinib.

I+V is an effective regimen which prolongs PFS, offers deep and durable responses and addresses the unmet need in CLL by being the first all-oral, once daily, chemotherapy-free, FD regimen that patients can take at home, without the need for infusion-based hospital treatments.

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify relevant clinical evidence on efficacy and safety of treatments for untreated CLL, published between 2011 and 2022.

A broad SLR was conducted, capturing 92 publications. Seventeen randomised controlled trials (RCTs) reported across the 92 publications were relevant to decision-making in the UK (i.e., they reported evidence for either I+V or a relevant comparator in the first-line treatment setting, as defined in the PICOS table presented in Appendix D.1.2). Five of the trials were available only in conference proceedings and the remaining 12 were available in full-text publications. Most of the included RCTs were phase III, multicentre trials and were open-label in design. PFS was the most commonly assessed primary outcome, being evaluated in 10 RCTs, followed by CR. Very few studies reported complete information on the safety outcomes.

Five trials were identified which carried out analysis for patients with del17p/TP53 mutation. These RCTs reported either survival and/or response estimates for the high-risk population. All five RCTs were available in full-text publications and were phase III, multicentre trials. O-Clb was the most evaluated comparator, having been investigated in three of the five trials. PFS was the primary outcome assessed in all of the RCTs.

None of the identified publications reported on the safety profile for the treatments in the high-risk subgroup.

Only the studies including I+V or comparators of interest in the first-line setting underwent data extraction. Full details of the SLR search strategy, methodology and results are presented in Appendix D.1.1 through D.1.7.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified two clinical trials which provided comprehensive efficacy and safety data for I+V in first-line CLL, summarised in Table 8:

- CAPTIVATE (NCT02910583), a non-comparative phase II trial of I+V in the FCR-suitable population
- GLOW (NCT03462719), a randomised phase III trial of I+V vs. O-Clb in the FCR-unsuitable population

Table 8 Clinical effectiveness evidence

Study	**CAPTIVATE** (66, 68)	**GLOW** (67, 70, 72)
Study design	International, multi-centre, phase II, 2-cohort clinical trial, including the FD cohort (the focus of this submission for CAPTIVATE) and the MRD cohort	International, multi-centre, open-label, phase III randomised clinical trial
Population	FD cohort: • Age ≥18 and ≤70 years • Diagnosis of CLL/SLL meeting iwCLL criteria(39) • Active disease requiring treatment per iwCLL criteria(39) • Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm by longest diameter • ECOG PS ≤2 • No prior therapy for CLL or SLL • No suspected Richter's syndrome	• Age ≥65 years, **or** 18 to 64 years of age with CIRS score >6 and/or CrCl <70 mL/min • Diagnosis of CLL/SLL meeting iwCLL criteria(39) • Active disease requiring treatment per iwCLL criteria(39) • Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm by longest diameter • ECOG PS ≤2 • No prior anti-leukaemic therapy for CLL or SLL • No del17p or known TP53 mutation • No CNS involvement or suspected Richter's syndrome

Study	**CAPTIVATE** (66, 68)		**GLOW** (67, 70, 72)	
Intervention(s)	I+V		I+V	
Comparator(s)	None		O-Clb	
Study supports application for marketing authorisation?	Yes	✓	Yes	✓
Study used in the economic model?	Yes	✓[a]	Yes	✓
Rationale if study not used in the model	Not applicable		Not applicable	
Reported outcomes specified in the decision problem[b]	• **PFS** • **OS** • **AEs**		• **PFS** • **OS** • **AEs** • **HRQoL**	
All other reported outcomes	• MRD negative rate • CR/CRi rate • ORR • Rate of sustained haematological improvement • DOR • Reduction of TLS risk • Response to ibrutinib reintroduction following disease progression		• MRD negative rate • CR/CRi rate • ORR • Rate of sustained haematological improvement • Time to first meaningful improvement in FACIT-Fatigue score • DOR • Reduction of TLS risk	

AE = adverse event; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CNS = central nervous system; CR = complete response; CrCl = creatinine clearance; CRi = complete response with incomplete bone marrow recovery; CT = computerised tomography; del17p = 17p deletion; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FD = fixed duration; FISH = fluorescent in situ hybridisation; O-Clb = obinutuzumab + chlorambucil; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; SLL = small lymphocytic lymphoma; TLS = tumour lysis syndrome; TP53 = tumour protein 53

[a] Only the FD cohort is used in the economic model.

[b] Outcomes that are incorporated into the model are bolded. Note that OS is not directly used in the model, but is used for validation.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The methodology of the phase II CAPTIVATE study (FD cohort) and the phase III GLOW study is summarised in Table 9.

Table 9 Summary of trial methodology

Trial	**CAPTIVATE** (66, 68, 73)	**GLOW** (67, 70, 72)
Location	[redacted] centres across [redacted] countries in Europe, North America and Asia-Pacific	67 centres across 14 countries in Europe and North America
Trial design	Multi-centre, two-cohort, phase II trial, including one cohort (the FD cohort) that evaluated the efficacy and safety of an oral FD I+V combination regimen in patients with previously untreated CLL/SLL who met iwCLL criteria for active treatment	Randomised, open-label, multi-centre phase III study to evaluate the efficacy and safety of the oral I+V combination regimen vs. O-Clb in patients with previously untreated CLL/SLL who met iwCLL criteria for active treatment
Eligibility criteria	FD cohort: • Age ≥18 and ≤70 years • Diagnosis of CLL/SLL meeting iwCLL criteria(39) • Active disease requiring treatment per iwCLL criteria(39) • Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm by longest diameter • ECOG PS ≤2 • No prior therapy for CLL or SLL • No suspected Richter's syndrome	• Age ≥65 years, **or** 18 to 64 years of age with CIRS score >6 and/or CrCl <70 mL/min • Diagnosis of CLL/SLL meeting iwCLL criteria(39) • Active disease requiring treatment per iwCLL criteria(39) • Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm by longest diameter • ECOG PS ≤2 • No prior anti-leukaemic therapy for CLL or SLL • No del17p or known TP53 mutation • No CNS involvement or suspected Richter's syndrome
Trial drugs	In the FD cohort (n=159): • Ibrutinib (420 mg/day orally) for 15 cycles • Venetoclax with dose ramp-up (20 mg/day to 400 mg/day over 5 weeks, then 400 mg/day, orally) from Cycle 4 to Cycle 15	In the I+V group (n=106): • Ibrutinib (420 mg/day orally) for 15 cycles • Venetoclax with dose ramp-up (20 mg/day to 400 mg/day orally over 5 weeks, then 400 mg/day) from Cycle 4 to Cycle 15 In the O-Clb group (n=105): • Obinutuzumab (1,000 mg IV) on Days 1, 8 and 15 of Cycle 1 and Day 1 of Cycles 2 to 6

Trial	**CAPTIVATE** (66, 68, 73)	**GLOW** (67, 70, 72)
		• Chlorambucil (0.5 mg/kg orally) on Days 1 and 15 of Cycles 1 to 6
Permitted and disallowed concomitant medication	Permitted concomitant therapies: • Supportive therapy (i.e., fluids, electrolyte replacement, antibiotics, emetics) • Neutrophil growth factors • Red blood cell growth factors • Transfusions • Localised hormonal or bone sparing treatment for non-B-cell malignancies • Localised radiotherapy for medical conditions other than underlying B-cell malignancies • Short courses of steroid treatment for <14 days for non-cancer related medical reasons (≤100 mg/day of prednisone or its equivalent) • Treatment for autoimmune cytopenias for <14 days at ≤100 mg/day of prednisone or its equivalent Prohibited concomitant therapies: • Non-study chemotherapy, anticancer immunotherapy, experimental therapy or radiotherapy for the underlying B-cell malignancy with ibrutinib • Corticosteroids for the underlying malignancy • Strong cytochrome P450 3A inhibitors during administration of the venetoclax ramp-up doses • Warfarin or vitamin K antagonists concomitantly with ibrutinib • Fish oil and vitamin E preparations	Permitted concomitant therapies: • Supportive therapy (i.e., IV fluids) • Growth factors (e.g., filgrastim) • Blood product transfusions • Anti-microbial prophylaxis • Short courses of corticosteroids for <14 days for non-cancer related medical reasons (≤100 mg/day of prednisone or its equivalent) Prohibited concomitant therapies: • Non-study anti-leukaemic treatment in patients who had not progressed • Corticosteroids at dosages equivalent to prednisone >20 mg/day for >14 days in patients who had not progressed • Live vaccines during the study treatment phase • Strong cytochrome P450 3A inhibitors during administration of the venetoclax ramp-up doses • Warfarin and vitamin K antagonists concomitantly with ibrutinib

Trial	**CAPTIVATE** (66, 68, 73)	**GLOW** (67, 70, 72)
Primary outcomes	Evaluation of the depth of response per CR/CRi rate following treatment with I+V in patients without del17p	Comparison of IRC-assessed PFS, defined as the duration from randomisation to disease progression or death, between the I+V and the O-Clb groups
Other outcomes specified in the scope	• OS • PFS • MRD • AEs	• OS • Response rates (including CR/CRi) • MRD • AEs • HRQoL
Pre-planned subgroups	Prespecified supporting analysis: • All treated patients regardless of del17p status For CR/CRi and MRD only: • Age • Gender • Race • Rai stage at screening • Baseline ECOG PS • Bulky disease status • del17p status • del17p/TP53 mutation status • FISH abnormalities • IGHV mutation status	• Age • Gender • Race • Disease diagnosis at baseline • Disease stage at screening • Baseline ECOG PS • CIRS total score • Bulky disease status • IGHV mutation status • del11q status • LDH at baseline • Cytopenia at baseline • Serum β2-microglobulin level at baseline

AE = adverse event; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CNS = central nervous system; CR = complete response; CrCl = creatinine clearance; CRi = complete response with incomplete bone marrow recovery; CT = computerised tomography; del11q = 11q deletion; del17p = 17p deletion; ECOG = Eastern Cooperative Oncology Group; FD = fixed duration; HRQoL = health-related quality of life; I+V = ibrutinib + venetoclax; IGHV = immunoglobulin heavy chain variable region; IRC = Independent Review Committee; IV = intravenous; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; LDH = lactic acid dehydrogenase; MRD = minimal residual disease; O-Clb = obinutuzumab + chlorambucil; OS = overall survival; PFS = progression-free survival; PS = performance status; SLL = small lymphocytic lymphoma

B.2.3.1 CAPTIVATE

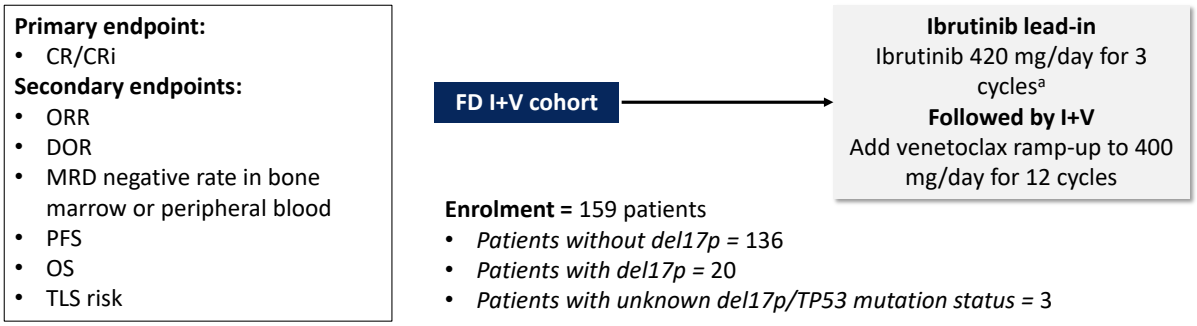
Trial design

CAPTIVATE was a multi-centre, phase II trial in two cohorts of patients with previously untreated CLL/SLL:(73)

- The **FD cohort** was an open-label, one-group cohort designed to evaluate the depth of response per CR/CRi following I+V combination therapy for a fixed duration.
- The **MRD cohort** included three phases (a pre-randomisation phase with I+V, an MRD-guided randomisation phase with therapy reintroduction, and a post disease progression follow-up phase) designed to evaluate the effect on 1-year disease-free survival of discontinuing ibrutinib therapy in patients who achieved MRD negativity.

The focus of this submission is the FD cohort because it is in line with how I+V will be administered in clinical practice. An overview of the CAPTIVATE trial design is depicted in Figure 3.

Figure 3 Trial design (CAPTIVATE FD cohort)



CR = complete response; CRi = complete response with incomplete bone marrow recovery; del17p = 17p deletion; DOR = duration of response; FD = fixed duration; I+V = ibrutinib + venetoclax; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TLS = tumour lysis syndrome
a One cycle = 28 days
Source: Pharmacyclics [Data on File], 2019(73)

Patient eligibility

Eligible patients enrolled into the FD cohort of the CAPTIVATE study were adults aged ≤70 years who had previously untreated CLL/SLL that met iwCLL criteria for active disease requiring treatment.(73) Patients in the FD cohort were enrolled

sequentially after the MRD cohort and included a total of 159 patients of which 136 patients without del17p.(66) The full eligibility criteria are summarised in Appendix M.1.1.

Settings and locations of data collection

The CAPTIVATE study FD cohort was conducted in [redacted] centres across [redacted] countries in Europe [redacted], North America (US) and Asia-Pacific [redacted].(68)

Trial drugs

Participants in the FD cohort of the CAPTIVATE study received ibrutinib monotherapy (420 mg/day orally) as a lead-in treatment for three cycles. A dose ramp-up for venetoclax was initiated (from 20 mg/day to 400 mg/day orally over 5 weeks) from Cycle 4. Treatment with venetoclax was continued (400 mg/day orally) in combination with ibrutinib (420 mg/day orally) for 12 cycles, until Cycle 15 unless discontinued early for toxicity. Venetoclax and ibrutinib were administered at the same time (or within 60 minutes) each day with a meal and water. After administration of the first dose of ibrutinib and after completion of the 5-week venetoclax dose ramp-up, each drug was typically administered on an outpatient basis.(73)

Participants who had disease progression per iwCLL criteria after completion of the FD I+V regimen could be retreated with continuous ibrutinib monotherapy until disease progression or unacceptable toxicity. Those with durable efficacy after I+V could be retreated with the I+V FD treatment regimen per investigator (INV) clinical discretion and Medical Monitor's approval.(73) No patients in the FD cohort had been retreated with I+V as of April 2022.(69) Safety results for patients retreated with ibrutinib monotherapy are presented in B.2.10.1 Subsequent therapy.

Dose modification of ibrutinib was recommended following development of liver impairment and was mandated in response to the following(73):

- Haematological events (absolute neutrophil count [ANC] <500 cells/μL for >7 days, platelets <50,000 cells/μL in the presence of clinically significant bleeding or platelets <25,000 cells/μL)

- Gastrointestinal events (grade 3 nausea, grade 3/4 vomiting or grade 3/4 diarrhoea if persistent despite optimal anti-emetic or anti-diarrhoeal therapy)
- Any other grade 4 or unmanageable grade 3 toxicity.

Dose modification of venetoclax was recommended in response to blood chemistry changes or symptoms suggestive of TLS, grade 3 or 4 non-haematologic toxicities and haematologic toxicities (ANC <1,000 cells/μL with infection or fever, ANC <500 cells/μL, platelets <25,000 cells/μL and haemoglobin levels <8 g/dL).(73)

The risks and benefits of ibrutinib treatment were to be considered in case of grade 3 or 4 atrial fibrillation or any grade persistent atrial fibrillation. Ibrutinib could be temporarily held in case of leukocytosis/leukostasis.(73)

Study outcomes

The primary endpoint for the FD cohort in the CAPTIVATE study was the depth of response per CR/CRi following treatment with the FD I+V combination regimen. The primary analysis was conducted when a clinically meaningful evaluation of durable CR rate (≥12 months) was possible for the study cohort.(73)

Secondary endpoints for the FD cohort in the CAPTIVATE study included the following:(73)

- Overall response rate (ORR) defined as the proportion of participants who achieve a response (CR, CRi, nodular partial response [PR], PR or PR with lymphocytosis per iwCLL 2008 criteria)
- Duration of response (DOR) defined as the interval between achievement of response (CR, CRi, nodular PR or PR per iwCLL response criteria, including PR with lymphocytosis) and disease progression or death from any cause
- MRD negative rate (<1 CLL cell per 10,000 leukocytes) by flow cytometry in BM or PB
- PFS from the date of first study treatment dose until disease progression (per iwCLL 2008 criteria) or death from any cause
- Overall survival (OS) from the date of first study treatment dose to death from any cause

- Reduction of TLS risk from baseline to after the ibrutinib lead-in dosing, based on tumour burden, with TLS risk/burden categories defined based on lymph node size and absolute lymphocyte count (ALC):
  - Low: all lymph nodes <5 cm and ALC <25 x 10^9/L
  - Medium: any lymph node 5 to <10 cm or ALC ≥25 x 10^9/L
  - High: any lymph node ≥10 cm, or ALC ≥25 x 10^9/L and any lymph node ≥5 cm
- Safety and tolerability

Exploratory endpoints for the FD cohort were as follows:(73)

- Rate of sustained haemoglobin improvement (haemoglobin levels [redacted]
- Rate of sustained platelet improvement (platelet counts [redacted]
- Response to ibrutinib reintroduction following disease progression

Baseline patient and disease characteristics

A total of 159 participants were included in the FD cohort, of which 147 completed planned ibrutinib treatment and 149 completed planned venetoclax treatment.(66) Additional information on patient disposition in the FD cohort of the CAPTIVATE study can be found in Appendix D.2.1.

The all treated population (n=159) included 129 patients without del17p or TP53 mutation, 27 patients with del17p or TP53 mutation (including 20 with del17p) and 3 patients with unknown del17p or TP53 mutation status.(66) The population of patients in the FD cohort without del17p (n=136; excluding 20 patients with del17p and 3 patients with unknown del17p or TP53 mutation status) is used for most analyses in this submission.

The populations including and excluding del17p were generally similar in terms of baseline characteristics (Table 10). The median age of the patients without del17p was [redacted] years (range [redacted] to [redacted] years); [redacted] participants were ≥65

years old [redacted].(68) [redacted] the participants were male [redacted], and [redacted] were white [redacted].(68)

[redacted] of patients without del17p in the FD cohort had an initial diagnosis of CLL and all patients had ECOG PS 0 [redacted] or 1 [redacted]. Among patients without del17p, the proportions of patients with TP53 mutation, chromosome 11q deletion (del11q) and immunoglobulin heavy chain variable region (IGHV) mutation were [redacted] respectively.(68)

Table 10 Characteristics of participants in the FD cohort (CAPTIVATE; all treated population)

CAPTIVATE Baseline characteristic[a]	Non-del17p (68)	All treated (66, 68, 74)
Patients, n	**n=136**	**N=159**
Age		
Median years (range)	[redacted]	60.0 (33, 71)
Mean years (SD)	[redacted]	[redacted]
<65 years, n (%)	[redacted]	114 (71.7)
≥65 years, n (%)	[redacted]	45 (28.3)
Sex (%)		
Male, n (%)	[redacted]	106 (66.7)
Race, n (%)		
Asian	[redacted]	3 (1.9)
Black or African American	[redacted]	1 (0.6)
Native Hawaiian or Other Pacific Islander	[redacted]	1 (0.6)
White	[redacted]	147 (92.5)
Not reported	[redacted]	7 (4.4)
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	5 (3.1)
Not Hispanic or Latino	[redacted]	149 (93.7)
Not reported	[redacted]	5 (3.1)
Diagnosis, n (%)		
CLL	[redacted]	146 (91.8)
SLL	[redacted]	13 (8.2)
Time from initial diagnosis to randomisation in months		
Median (range)	[redacted]	[redacted]
Rai stage		
Stage 0/I/II, n (%)	[redacted]	113 (71.1)
Stage III/IV, n (%)	[redacted]	44 (27.7)
Missing	[redacted]	2 (1.3)
ECOG PS, n (%)		
0	[redacted]	110 (69.2)
1	[redacted]	49 (30.8)
Bulky disease[b]		
≥5 cm, n (%)	[redacted]	48 (30.2)
≥10 cm, n (%)	[redacted]	5 (3.1)

CAPTIVATE Baseline characteristic[a]	Non-del17p (68)	All treated (66, 68, 74)
Patients, n	**n=136**	**N=159**
Cytopenia, n (%)		
Haemoglobin ≤110 g/L	[redacted]	37 (23.3)
Platelets ≤100 x 10^9 /L	[redacted]	21 (13.2)
Absolute neutrophil count ≤1.5 x 10^9 /L	[redacted]	13 (8.2)
Any of the above	[redacted]	54 (34.0)
del17p or TP53 mutation, n (%)		
Yes	[redacted]	27 (17.0)
No	[redacted]	129 (81.1)
Unknown	[redacted]	3 (1.9)
TP53 mutation, n (%)		
Yes	[redacted]	16 (10.1)
No	[redacted]	142 (89.3)
Unknown	[redacted]	1 (0.6)
del17p, n (%)		
Yes	0	20 (12.6)
del11q, n (%)		
Yes	[redacted]	28 (17.6)
IGHV, n (%)		
Mutated	[redacted]	66 (41.5)
Unmutated	[redacted]	89 (56.0)
Unknown	[redacted]	4 (2.5)

CLL = chronic lymphocytic leukaemia; del11q = 11q deletion; del17p = 17p deletion; ECOG = Eastern Cooperative Oncology Group; IGHV = immunoglobulin heavy chain variable region; INV = investigator; SLL = small lymphocytic lymphoma; TP53 = tumour protein p53

[a] Baseline is defined as the last measurement taken on or prior to first dose date of study treatment.

[b] Bulky disease is based on the largest longest diameter of target lymph node at screening per INV assessmentSource: Pharmacyclics [Data on File], 2021(68); Wierda, 2022(69)

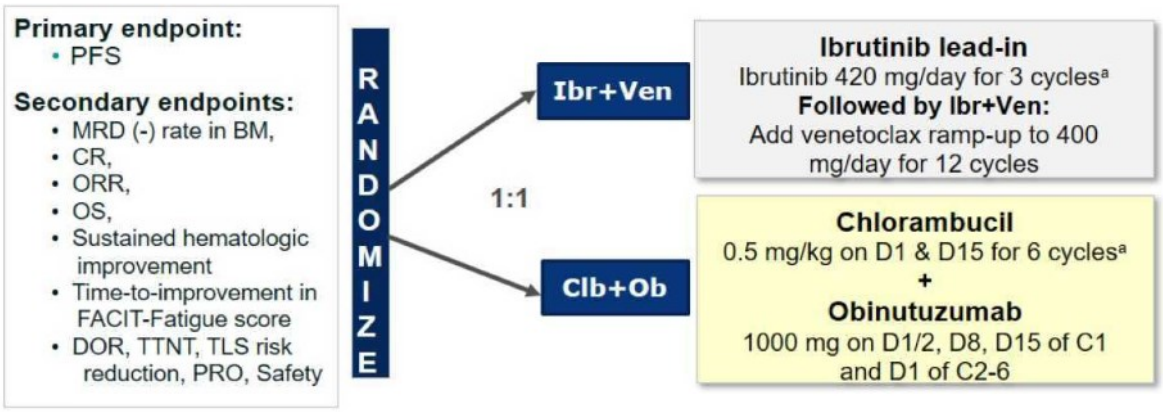
B.2.3.2 GLOW

Trial design

GLOW is a randomised, open-label, multi-centre, phase III trial in patients with previously untreated CLL/SLL who met iwCLL treatment criteria and were suitable for treatment with O-Clb but not a more intense fludarabine-containing regimen.(67, 70) The primary objective of the study was to evaluate IRC-assessed PFS for patients randomised 1:1 to combination therapy with I+V vs. O-Clb.(67)

An overview of the GLOW trial design is depicted in Figure 4.

Figure 4 Trial design (GLOW)



Enrolment = 211 patients
- *Patients randomised to Ibr+Ven* = 106
- *Patients randomised to O-Clb* = 105

Stratification:
- IGHV status (mutated vs. unmutated vs. not available)
- Del11q (yes vs. no)

BM = bone marrow; C = cycle; Clb+Ob = chlorambucil + obinutuzumab; CR = complete response; D = day; del11q = 11q deletion; DOR = duration of response; Ibr+Ven = ibrutinib + venetoclax; IGHV = immunoglobulin heavy chain variable region; MRD = minimal residual disease; O-Clb = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; TLS = tumour lysis syndrome; TTNT = time to next treatment
[a] One cycle = 28 days
Source: Janssen Research & Development LLC [Data on File], 2021(70)

Patient eligibility

Eligible patients in GLOW were aged ≥65 years, **or** 18 to 64 years with CIRS score >6 and/or estimated CrCl <70 mL/min.(67) Included patients had previously untreated CLL/SLL that met iwCLL criteria for active disease requiring treatment.(67) The full eligibility criteria are summarised in Appendix M.2.1.

Settings and locations of data collection

The GLOW study was conducted in 67 centres across 14 countries in Europe and North America, including eight centres in the UK.(67)

Trial drugs

Participants in the GLOW study were randomised 1:1 to receive either FD I+V or O-Clb, with randomisation stratified by IGHV status and del11q.(67)

In the I+V group, participants received ibrutinib monotherapy (420 mg/day orally) as a lead-in treatment for three cycles.(67) A dose ramp-up for venetoclax was initiated (from 20 mg/day to 400 mg/day orally over 5 weeks) from Cycle 4, following a risk

assessment for TLS.(67, 70) Treatment with venetoclax was continued (400 mg/day orally) in combination with ibrutinib (420 mg/day orally) for 12 cycles, until Cycle 15, in the absence of progressive disease or treatment-limiting toxicity.(67, 70) During cycles with combination dosing, ibrutinib and venetoclax were to be taken at the same time with a glass of water and a meal.(70) After the 5-week ramp-up, the I+V regimen was typically administered on an outpatient basis.(72)

Similar dose modifications of ibrutinib and venetoclax were permitted in GLOW as in CAPTIVATE (described in the Trial Drugs section above).

In the O-Clb group, participants received six cycles of obinutuzumab (1,000 mg IV on Days 1, 8 and 15 of Cycle 1 and 1,000 mg IV on Day 1 of Cycles 2 to 6) in combination with chlorambucil (0.5 mg/kg orally on Days 1 and 15 of Cycles 1 to 6).(70) The first 1,000 mg dose of obinutuzumab could be split over 2 days if patients did not tolerate the first 100 mg given IV on Day 1, in which case the remaining 900 mg was administered IV on Day 2. The O-Clb regimen was generally administered in the healthcare clinic; on days in which chlorambucil was administered alone (i.e., Day 15 of Cycles 2 to 6 only), chlorambucil could either have been given in the clinic or issued to the patient for administration at home.(72)

In the O-Clb group, premedication for infusion-related reactions and TLS was recommended, and dose delays of obinutuzumab were allowed in response to any toxicity meriting a dose delay in the opinion of the INV, including active infection, severe or life-threatening cytopenia or grade ≥2 non-haematologic toxicity. Dose reductions of obinutuzumab were not permitted. Dose modifications of chlorambucil were allowed in response to cytopenia (defined as one of the following: ANC <500 cells/μL for ≥7 days, platelets <50,000 cells/μL in the presence of bleeding, platelets <25,000 cells/μL or haemoglobin levels <8 g/dL) and grade 3 or 4 unmanageable non-haematologic toxicity.(72)

If a medicine was discontinued due to toxicity, the other medicine in the combination regimen could be continued.(72)

In the subsequent therapy phase (after completion of FD treatment regimens with I+V or O-Clb), participants in either treatment group who developed IRC-confirmed progressive disease following first-line treatment and had active disease requiring

treatment may have been eligible to receive ibrutinib monotherapy until progressive disease or unacceptable toxicity per INV assessment.(70, 72) Safety results for patients retreated with ibrutinib monotherapy are presented in B.2.10.2 Subsequent therapy.

Study outcomes

The primary endpoint for the GLOW study was IRC-assessed PFS (defined as the time between randomisation and the first instance of either progressive disease or death due to any cause) for I+V vs. O-Clb.(67) PFS was also evaluated based on progressive disease (PD) assessed by INV.(67)

Secondary objectives in the GLOW study included efficacy, safety and pharmacokinetic outcomes.(67) The following key secondary efficacy endpoints were tested hierarchically in the following order:(67, 70)

- MRD negative rate (<1 CLL cell per 10,000 leukocytes) by next generation sequencing (NGS) in BM (primary MRD analysis for hierarchical testing) and PB (supportive analysis)
- CR (with or without incomplete marrow recovery) prior to initiation of subsequent anti-leukaemic therapy, including ibrutinib monotherapy, per IRC assessment
- ORR (defined as the proportion of participants who achieved a best overall response of either CR, CRi, nodular PR, or PR per iwCLL criteria) on or prior to initiation of subsequent anti-leukaemic therapy, including ibrutinib monotherapy, per IRC assessment
- OS from the date of randomisation to death from any cause
- Rate of sustained platelet improvement (platelet counts increased ≥50% over baseline for ≥56 days without blood transfusion or growth factors)
- Rate of sustained haemoglobin improvement (haemoglobin levels increased ≥2 g/dL from baseline for ≥56 days without blood transfusion or growth factors)

- Time to first meaningful improvement in Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) score

Other secondary endpoints for the GLOW study were:(67, 70, 72)

- DOR defined as the interval between achievement of response (CR, CRi, nodular PR or PR per iwCLL response criteria, including PR with lymphocytosis) and disease progression or death from any cause
- Time to next anti-leukaemic therapy subsequent to study treatment from randomisation (TTNT)
- Reduction of TLS risk from baseline to after the ibrutinib lead-in dosing, based on tumour burden, with TLS risk/burden categories defined based on lymph node size and ALC:
  - Low: all lymph nodes <5 cm and ALC <25 x 10^9/L
  - Medium: any lymph node 5 to <10 cm or ALC ≥25 x 10^9/L
  - High: any lymph node ≥10 cm, or ALC ≥25 x 10^9/L and any lymph node ≥5 cm; any lymph node size and ALC and CrCl ≤50 mL/min
- Time to first meaningful deterioration in functional status per the EuroQoL-5 Dimension-5 Levels (EQ-5D-5L) questionnaire and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

Safety parameters included AEs and laboratory tests.(70, 72)

Baseline patient and disease characteristics

A total of 211 participants were randomised and included in the intent-to-treat (ITT) population of GLOW (I+V: n=106; O-Clb: n=105).(67) Additional information on patient disposition in the GLOW study can be found in Appendix D.2.2.

Demographic characteristics were well balanced between the treatment groups and reflected the target population of elderly and unfit patients with previously untreated CLL who were suitable for treatment with O-Clb but not a more intense fludarabine-containing regimen (Table 11).(70) The median age of the patient population was 71 years (range 47 to 93 years); approximately one third of participants were ≥75 years

old (34.1%). Over half of the participants were male (57.8%) and the majority were white (95.7%).(67, 70, 75)

Baseline disease characteristics were generally balanced between the treatment groups, except for CIRS score >6 and lactic acid dehydrogenase (LDH) elevation, both of which had a >10% difference between the groups (Table 11). The majority of participants had an initial diagnosis of CLL (93.4%) and over half had high-risk disease (58.3%; defined as those with TP53 mutation, del11q or unmutated IGHV).(67, 70)

Note that while patients with known TP53 mutation were excluded from GLOW, the inclusion criteria did not require testing, meaning that patients with unknown TP53 mutation status could still enrol in the trial. After randomisation, central testing identified 9 (4.3%) patients with a TP53 mutation (including 7 in the I+V group and 2 in the O-Clb group).(67) Although TP53 mutation is a strong negative prognostic factor for O-Clb, the impact on results of 2 patients having the mutation should be minimal.

Table 11 Characteristics of participants in the studies across treatment groups (GLOW; ITT)

GLOW Baseline characteristic[a]	**I+V**	**O-Clb**	**Total**
Patients, n	**n=106**	**n=105**	**N=211**
Age			
Median years (range)	71.0 (47, 93)	71.0 (57, 88)	[redacted]
Mean years (SD)	71.0 (8.02)	72.0 (6.16)	71.5 (7.15)
<65 years, n (%)	16 (15.1)	11 (10.5)	27 (12.8)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
≥75, n (%)	35 (33.0)	37 (35.2)	[redacted]
Sex (%)			
Male, n (%)	59 (55.7)	63 (60.0)	122 (57.8)
Race, n (%)			
Asian	0 (0)	1 (1.0)	1 (0.5)
White	101 (95.3)	101 (96.2)	202 (95.7)
Multiple	1 (0.9)	0 (0)	1 (0.5)
Not reported	4 (3.8)	3 (2.9)	7 (3.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.9)	3 (2.9)	4 (1.9)
Not Hispanic or Latin	101 (95.3)	99 (94.3)	200 (94.8)
Not reported	4 (3.8)	3 (2.9)	7 (3.3)

GLOW Baseline characteristic[a]	I+V	O-Clb	Total
Patients, n	**n=106**	**n=105**	**N=211**
Diagnosis, n (%)			
CLL	96 (90.6)	101 (96.2)	197 (93.4)
SLL	10 (9.4)	4 (3.8)	14 (6.6)
Time from initial diagnosis to randomisation in months			
Median (range)	35.8 (0.5, 227.8)	35.4 (0.7, 178.8)	[redacted]
Binet stage (CLL only)			
N	96	101	197
Binet stage A, n (%)	7 (7.3)	8 (7.9)	15 (7.6)
Binet stage B, n (%)	46 (47.9)	53 (52.5)	99 (50.3)
Binet stage C, n (%)	43 (44.8)	40 (39.6)	83 (42.1)
ECOG PS, n (%)			
0	35 (33.0)	39 (37.1)	74 (35.1)
1-2	71 (67.0)	66 (62.9)	137 (64.9)
CIRS total score, n (%)			
≤6	32 (30.2)	44 (41.9)	76 (36.0)
>6	74 (69.8)	61 (58.1)	135 (64.0)
Bulky disease			
N	105	105	210
≥5 cm, n (%)	41 (39.0)	38 (36.2)	79 (37.6)
Cytopenia, n (%)[b]			
Yes	58 (54.7)	65 (61.9)	123 (58.3)
TP53 mutation, n (%)			
Yes	7 (6.6)	2 (1.9)	9 (4.3)
del11q, n (%)			
Yes	20 (18.9)	18 (17.1)	38 (18.0)
IGHV, n (%)			
Mutated	27 (25.5)	27 (25.7)	54 (25.6)
Unmutated	55 (51.9)	54 (51.4)	109 (51.7)
Unavailable	24 (22.6)	24 (22.9)	48 (22.7)
High-risk population[c], n (%)			
Yes	63 (59.4)	60 (57.1)	123 (58.3)
Elevated LDH, n (%)			
Yes (>ULN)	35 (33.0)	51 (48.6)	86 (40.8)
Serum β2-microglobulin, n (%)			
≤3.5 mg/L	32 (30.2)	27 (25.7)	59 (28.0)
>3.5 mg/L	74 (69.8)	77 (73.3)	151 (71.6)
Missing	0 (0)	1 (1.0)	1 (0.5)

CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; del11q = 11q deletion; ECOG = Eastern Cooperative Oncology Group; O-Clb = obinutuzumab + chlorambucil; IGHV = immunoglobulin heavy chain variable region; ITT = intent-to-treat; I+V = ibrutinib + venetoclax; LDH = lactic acid dehydrogenase; PS = performance status; SD = standard deviation; SLL = small lymphocytic lymphoma; TP53 = tumour protein 53; ULN = upper limit of normal

[a] Unless otherwise indicated, the number of participants evaluated was 106 for I+V group and 105 for the O-Clb group.

[b] Cytopenia was defined as one of the following: haemoglobin ≤110 g/dL, platelet counts ≤100 x 10^9/L or ANC ≤1.5 x 10^9/L.

[c] High-risk population was defined as the presence of any one of the following: TP53 mutation, del11q or unmutated IGHV.

Sources: Janssen Research & Development LLC [Data on File], 2021(70); Kater, 2022(67); Clinicaltrials.gov, 2022(75)

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

B.2.4.1 CAPTIVATE (FD cohort)

In CAPTIVATE, 159 participants were included in the FD cohort, as depicted in the CONSORT diagram in Appendix D.2.1.(66) This included 129 patients without del17p or TP53 mutation, 27 patients with del17p or TP53 mutation (including 20 with del17p) and 3 patients with unknown del17p or TP53 mutation status.(66) All 159 participants who received at least one dose of study treatment were analysed as part of the all treated population, which was used for efficacy and safety analyses.(66) Efficacy analyses of the 136 patients without del17p were also conducted.(66)

Primary analysis of CAPTIVATE was conducted based on a data cut-off date of 12 November 2020 (median 27.9 months follow-up).(66, 68) Analysis of extended follow-up data based on a data cut-off date of 4 August 2021 was also conducted to supplement the primary analysis with approximately 9 months of further follow-up (total 38.7 months follow-up).(68, 69) The extended follow-up data for the 136 patients without del17p informed the ITCs (B.2.9 Indirect and mixed treatment comparisons) and economic analysis (B.3 Cost effectiveness).

Statistical analyses undertaken in the phase II CAPTIVATE study are summarised in Table 12.

Table 12 Summary of statistical analyses (CAPTIVATE)

Trial	CAPTIVATE
Hypothesis objective	To evaluate the depth of response (CR/CRi) with the oral, FD combination therapy of I+V in patients with previously untreated CLL/SLL
Statistical analysis	The primary endpoint for the FD cohort in CAPTIVATE was CR/CRi rate per iwCLL criteria for the all treated population. Participants missing response assessments were classified as non-responders. The endpoint was evaluated using descriptive statistics and was assessed when there was a clinically meaningful duration of CR rate (≥12 months). Descriptive statistics were reported to summarise the data with number of observations, means, standard deviations, medians and ranges used for continuous variables and frequency and 95% CIs used for discrete variables. KM estimates were reported for time-to-event variables.
Sample size, power calculation	The FD cohort was powered to detect a CR rate of >37% at 83% power and a 1-sided significance level of 0.025, with the assumption that treatment with I+V would provide an actual CR rate of 50%, requiring approximately 125 participants to be enrolled in the cohort. A CR of 50% represents a clinically meaningful difference to the CR reported for a FD combination therapy of BR (31%) and would be an improvement over the 40% CR rate observed with the standard of care FD regimen of FCR in the CLL10 study, which included only patients without del17p.
Data management, patient withdrawals	Participants were classified as having withdrawn from the study when they were lost to follow-up, when they withdrew consent or when they died. The reason for withdrawal and the extent of any withdrawal of consent were recorded. All withdrawn participants underwent an End of Treatment Visit and were followed for progression and survival. An independent committee monitored the study until its completion to ensure the quality and integrity of the data.

BR = bendamustine +rituximab; CI = confidence interval; CLL = chronic lymphocytic leukaemia; CR = complete response; CRi = complete response with incomplete bone marrow recovery; del17p = 17p deletion; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; SLL = small lymphocytic lymphoma
Source: Pharmacyclics [Data on File], 2019(73); Tam, 2022(66)

B.2.4.2 GLOW

In the GLOW study, 211 participants were randomised 1:1 to the two treatment groups (106 in the I+V group and 105 in the O-Clb group), as depicted in the CONSORT diagram in Appendix D.2.2.(67, 70) All 211 randomised participants were

included in both the ITT population (used for all primary and secondary efficacy endpoints) and the safety population (defined as all randomised participants who received at least one dose of study drug).(67)

Primary analysis of GLOW was conducted based on a data cut-off date of 26 February 2021 (median 27.7 months follow-up). Analysis of extended follow-up data based on a data cut-off date of [redacted] was also conducted to supplement the primary analysis with approximately 6 months of further follow-up (total median 34.1 months follow-up).(67, 70) The extended follow-up data informed the ITCs (B.2.9 Indirect and mixed treatment comparisons) and economic analysis (B.3 Cost effectiveness).

Statistical analyses undertaken in the phase III GLOW study are summarised in Table 13.

Table 13 Summary of statistical analyses (GLOW)

Trial	GLOW
Hypothesis objective	Treatment with the combination of I+V will result in longer PFS compared with O-Clb in patients with previously untreated CLL
Statistical analysis	Comparison between the two treatment groups were performed using analysis of variance for continuous variables, Cochran-Mantel-Haenszel chi-square test for discrete variables and stratified log-rank test for time-to-event variables. All tests were conducted at a 2-sided alpha level of 0.05. KM methodology was used to estimate the distribution of PFS for each treatment group, with comparison between treatment groups by stratified log-rank test. The HR was calculated by a Cox regression model with stratification for IGHV mutation status and presence of del11q. Hierarchical testing was performed for key secondary efficacy endpoints (MRD negative rate by NGS, CR rate, ORR, OS, rate of sustained platelet improvement, rate of sustained haemoglobin improvement, and time to first meaningful improvement in FACIT-Fatigue score) to control for type I error.
Sample size, power calculation	The study was powered to evaluate the effect of treatment on PFS based on a report of a median PFS of 27 months for O-Clb when used as a first-line therapy for patients with CLL, with PFS assumed to follow an exponential distribution with constant hazard rate. Approximately 200 participants (100 per treatment group) were required to detect a HR of 0.5 (corresponding to 100% improvement in median PFS), with 80% power at a significance level of 0.05 and based on the observation of 71 PFS events.
Data management, patient withdrawals	Participants were classified as having withdrawn from the study when they were lost to follow-up or when they withdrew consent, with the reason for withdrawal documented in the electronic case report form. Discontinuation of study treatment did not result in automatic withdrawal of the participant and study assessments were still collected. An independent data monitoring committee evaluated the data at specific milestones to ensure the safety of participants.

CLL = chronic lymphocytic leukaemia; CR = complete response; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; HR = hazard ratio; I+V = ibrutinib + venetoclax; IRC = Independent Review Committee; KM = Kaplan-Meier; MRD = minimal residual disease; NGS = next generation sequencing; O-Clb = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SLL = small lymphocytic lymphoma

Sources: Janssen Research & Development LLC [Data on File], 2021(70); Janssen Research & Development LLC [Data on File], 2019(72)

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessment of CAPTIVATE (FD cohort) and GLOW, which are high-quality studies and are pertinent to the decision problem, is provided in Table 14 below. A detailed quality assessment of the CAPTIVATE and GLOW trials is provided in Appendix D.2.3.

Table 14 Quality assessment results

Trial	CAPTIVATE FD Cohort	GLOW
Was randomisation carried out appropriately?	N/A	Yes
Was the concealment of treatment allocation adequate?	N/A	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Yes
Were there any unexpected imbalances in drop-outs between groups?	N/A	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 CAPTIVATE (FD cohort)

Outcomes for the extended follow-up analysis (median 38.7 months follow-up) of the primary and secondary efficacy endpoints tested in the CAPTIVATE study FD cohort are summarised in Table 15. Appendix M.1.2 includes a similar summary of clinical effectiveness based on the primary analysis (median 27.9 months follow-up).

Primary and certain secondary endpoint (PFS, OS, reduction of TLS risk) results from both analyses of CAPTIVATE (all treated and non-del17p populations) are discussed in more detail in subsequent sections. Discussion of the other secondary endpoints and exploratory endpoints results is presented in Appendix M.1.4 and M.1.5, respectively.

Table 15 Summary of clinical effectiveness at a median follow-up of 38.7 months (CAPTIVATE FD cohort; extended follow-up analysis)

Endpoint	Assessment	Outcome	I+V, without del17p (n=136)	I+V, all treated (N=159)
Primary Endpoint				
Depth of response per CR/CRi	INV	Rate, % (95% CI)	58.1 (49.8, 66.4)	57.2 (49.5, 64.9)
	IRC	Rate, % (95% CI)	[redacted]	[redacted]
Secondary Endpoints				
ORR	INV	Rate, % (95% CI)	[redacted]	[redacted]
	IRC	Rate, % (95% CI)	[redacted]	[redacted]
DOR	INV	Median, months (95% CI)	[redacted]	[redacted]
		Rate at [redacted] months, % (95% CI)	[redacted]	[redacted]
	IRC	Median, months (95% CI)	[redacted]	[redacted]
		Rate at [redacted] months, % (95% CI)	[redacted]	[redacted]
MRD negative rate by flow cytometry	BM	Rate, % (95% CI)	[redacted]	[redacted]
	PB	Rate, % (95% CI)	[redacted]	[redacted]
PFS	INV	Median, months (95% CI)	[redacted]	NE (NE, NE)
		Rate at 36 months, % (95% CI)	[redacted]	88.1 (81.7, 92.3)
	IRC	Median, months (95% CI)	[redacted]	[redacted]
		Rate at [redacted] months, % (95% CI)	[redacted]	[redacted]
OS	Not applicable	Median, months (95% CI)	[redacted]	NE (NE, NE)
		Rate at [redacted] months, % (95% CI)	[redacted]	98.1 (94.2, 99.4)
Reduction of TLS risk	Not applicable	Proportion with high risk of TLS at baseline reduced to medium/low,[b] %	Not reported	94.1[c]

BM = bone marrow; CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; DOR = duration of response; I+V = ibrutinib + venetoclax; INV = investigator; IRC = Independent Review Committee; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; OS = overall survival; PB = peripheral blood; PFS = progression-free survival; TLS = tumour lysis syndrome

[redacted]

[b] After three cycles of ibrutinib monotherapy

[c] Results are presented based on the primary analysis; no analysis on reduction of TLS risk was conducted during extended follow-up

Source: Pharmacyclics [Data on File], 2021(68)

All treated patients and patients without del17p

Primary endpoint: depth of response per CR/CRi

As of the data cut-off for the primary analysis with a median follow-up of 27.9 months, the INV-assessed CR/CRi rate was 55.3% (95% CI: 47.6, 63.1) for all patients in the FD cohort and 55.9% (95% CI: 47.5, 64.2) for patients without del17p.(66) The CR/CRi rate for patients without del 17p was significantly higher than the study-assumed minimum rate of 37% ($p<0.0001$) as well as the 40% rate achieved in this population with FCR in the CLL10 study.(66, 76) Similar CR/CRi rates were observed for all patients and those without del17p with extended follow-up (median 38.7 months) (57.2% [95% CI: 49.5, 64.9] and 58.1% [95% CI: 49.8, 66.4], respectively).(68, 69) The majority (>86%) of CR/CRis were durable (defined as duration of CR/CRi for 12 months) based on INV assessment at the primary analysis and extended follow-up.(68)

[redacted] IRC-assessed CR/CRi was 59.7% (95% CI: 52.1, 67.4) for all patients in the FD cohort and 61.0% (95% CI: 52.8, 69.2) for patients without del17p at the primary analysis.(66) [redacted]

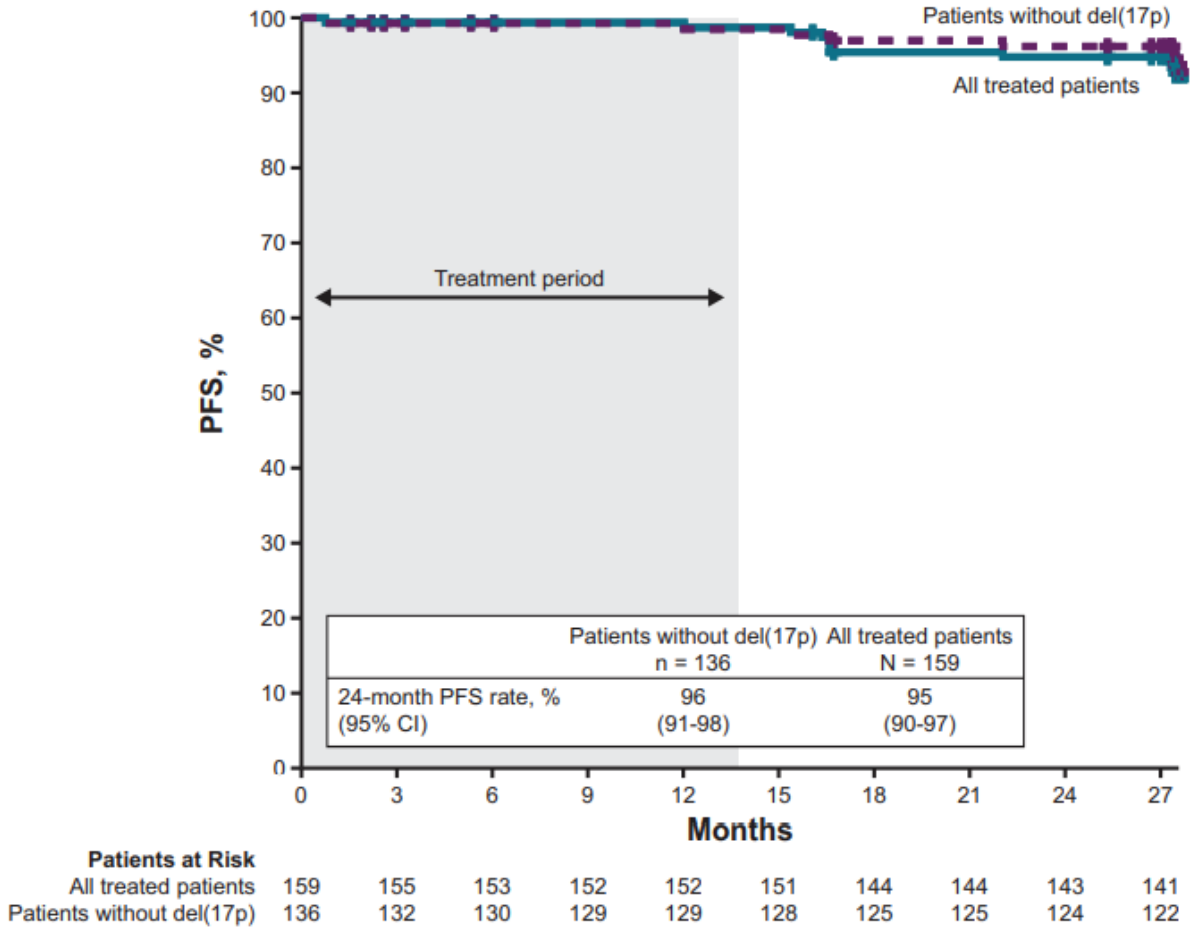
Results from the primary and extended follow-up analyses of CR/CRi and durable CR/CRi per INV and IRC assessments are presented in Appendix M.1.3. Subgroup analyses of CR/CRi rate are presented in B.2.7 Subgroup analysis.

Secondary endpoint: PFS

As of the data cut-off for the primary analysis with a median follow-up of 27.9 months, median INV-assessed PFS was not reached for all patients in the FD cohort(74) or for patients without del17p (Figure 5).(66) In the all treated population,

24-month PFS rates were high (97%-100%) regardless of clinical response (CR/CRi or PR/nPR) and MRD status in BM (undetectable or detectable) at 3 months after end of treatment.(66)

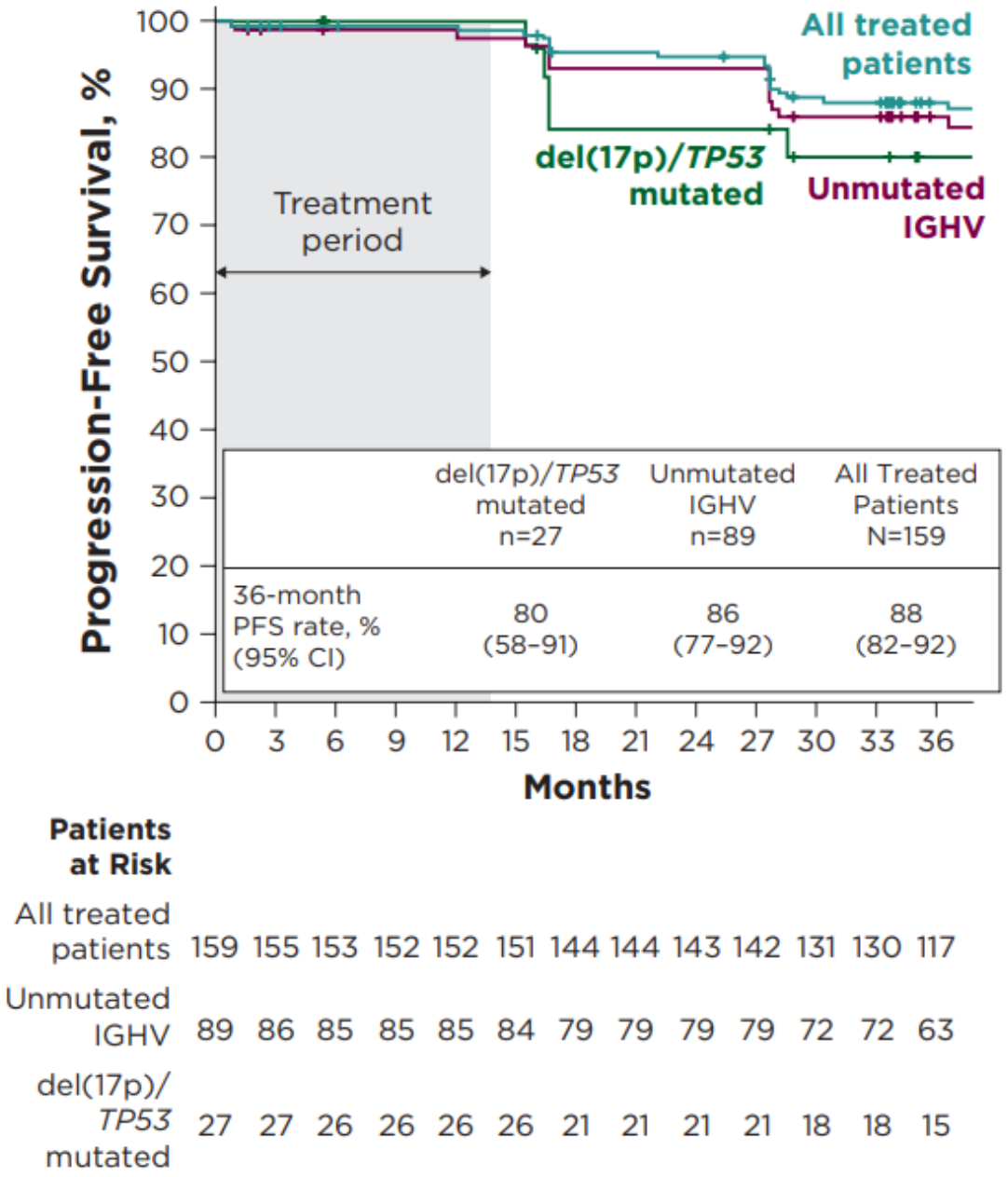
Figure 5 KM plot of INV-assessed PFS (CAPTIVATE; all treated population primary analysis)



CI = confidence interval; del17p = 17p deletion; INV = investigator; KM = Kaplan-Meier; PFS = progression-free survival
Note: Due to rapid enrolment in the study, the number of patients at risk drops substantially. The KM curve has therefore been truncated at 28 months due to instability of the curves.
Source: Tam, 2022(66)

At extended follow-up (median 38.7 months), median INV-assessed PFS was still not reached for all patients in the FD cohort (Figure 6) [redacted] (Figure 7).(68) The Kaplan-Meier (KM) point estimates for INV-assessed PFS at 36 months were 88.1% (95% CI: 81.7, 92.3) for all patients, [redacted] and 80% (95% CI: 58%, 91%) for high-risk patients.(68, 69)

Figure 6 KM plot of INV-assessed PFS (CAPTIVATE; all treated population extended follow-up)



CI = confidence interval; del17p = 17p deletion; IGHV = immunoglobulin heavy chain variable region; INV = investigator; KM = Kaplan-Meier; PFS = progression-free survival; TP53 = tumour protein p53
Note: Due to rapid enrolment in the study, the number of patients at risk drops substantially between 36 and 39 months. The KM curves have therefore been truncated at 38 months due to instability of the curves.
Source: Wierda, 2022(69)

Figure 7 KM plot of INV-assessed PFS (CAPTIVATE; all treated and no-del17p populations extended follow-up)

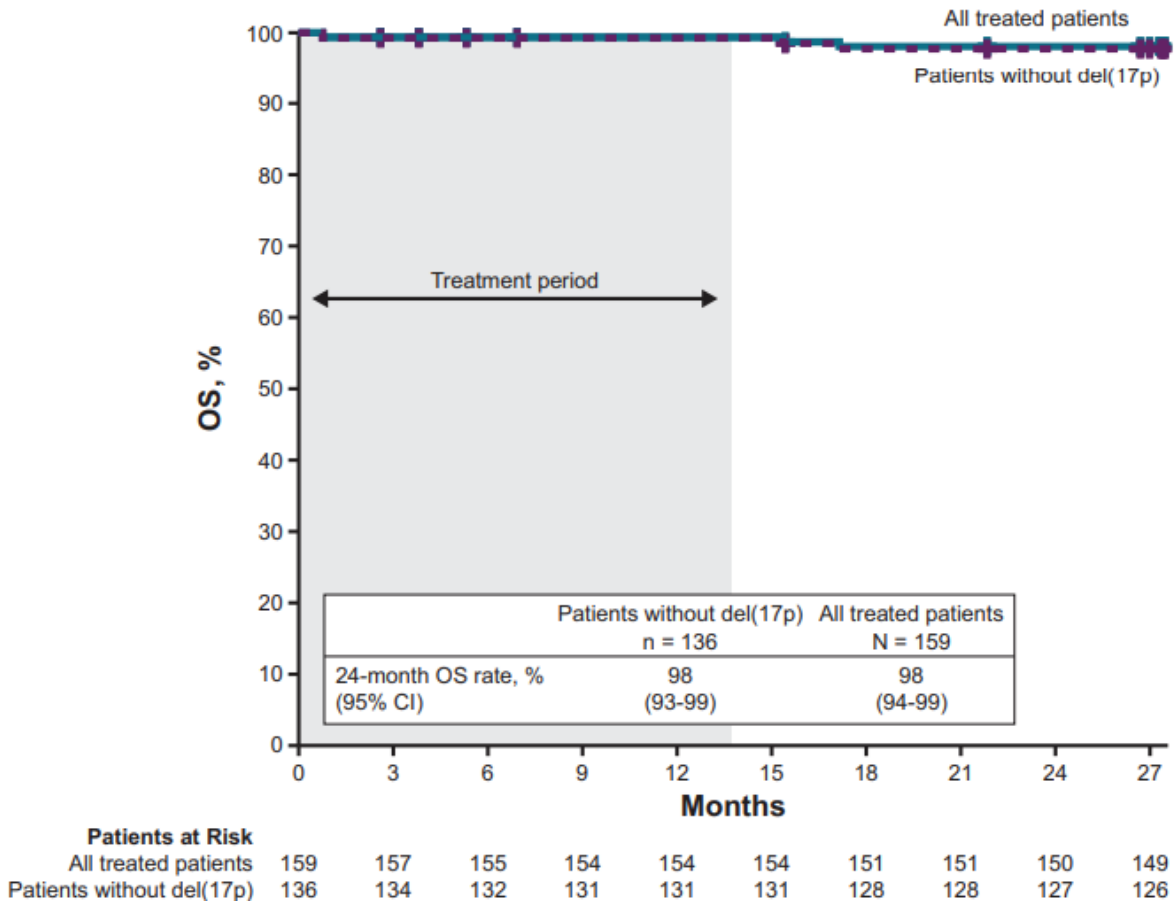
del17p = 17p deletion; FD = fixed duration; INV = investigator; KM = Kaplan-Meier; PFS = progression-free survival
Source: CAPTIVATE IPD

The median IRC-assessed PFS at the primary analysis The were for all patients and for patients without del17p and were therefore The KM plots of IRC-assessed PFS as of the primary analysis and at extended follow-up are shown in Appendix M.1.4.4.

Secondary endpoint: OS

As of the data cut-off for the primary analysis with a median follow-up of 27.9 months, median OS was not reached for all patients in the FD cohort(74) or for patients without del17p (Figure 8).(66, 68) A total of were reported due to and due to all of which occurred in .(68)

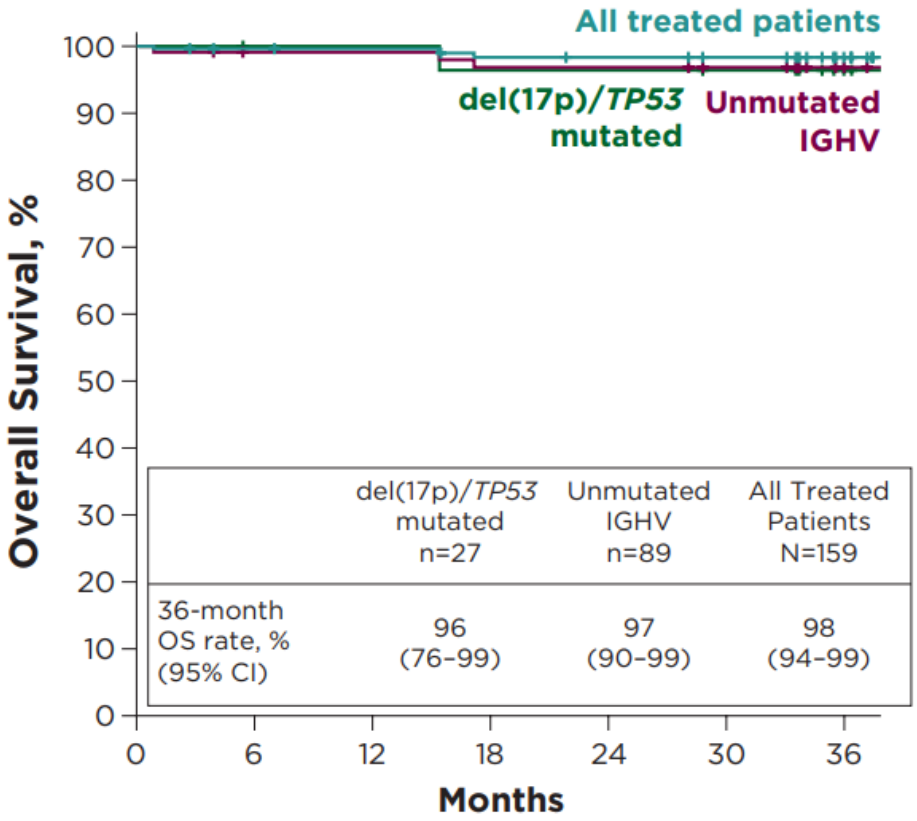
Figure 8 KM plot of OS (CAPTIVATE; all treated population primary analysis)



CI = confidence interval; del17p = 17p deletion; KM = Kaplan-Meier; OS = overall survival
Note: Due to rapid enrolment in the study, the number of patients at risk drops substantially. The KM curve has therefore been truncated at 28 months due to instability of the curves.
Source: Tam, 2022(66)

At extended follow-up (median 38.7 months), median OS was still not reached for all patients in the FD cohort (Figure 9) [redacted] (Figure 10), and no additional deaths occurred.(68) The KM point estimates at 36 months were 98.1% (95% CI: 94.2, 99.4) for all patients, [redacted] and 96% (95% CI: 76%, 99%) for high-risk patients.(68, 69)

Figure 9 KM plot of OS (CAPTIVATE; all treated population extended follow-up)



Patients at Risk							
All treated patients	159	155	154	151	150	148	139
Unmutated IGHV	89	86	86	84	84	82	75
del(17p)/*TP53* mutated	27	26	26	25	25	24	20

CI = confidence interval; del17p = 17p deletion; FD = fixed duration; IGHV = immunoglobulin heavy chain variable region; KM = Kaplan-Meier; OS = overall survival; TP53 = tumour protein p53
Note: Due to rapid enrolment in the study, the number of patients at risk drops substantially between 36 and 39 months. The KM curves have therefore been truncated at 38 months due to instability of the curves.
Source: Wierda, 2022(69)

Figure 10 KM plot of OS (CAPTIVATE; all treated and no-del17p populations extended follow-up)

CI = confidence interval; del17p = 17p deletion; FD = fixed duration; KM = Kaplan-Meier; OS = overall survival
Source: CAPTIVATE IPD

Secondary endpoint: reduction of TLS risk

The risk of TLS was reduced in patients who received lead-in treatment with ibrutinib monotherapy, based on high tumour burden.(66) Tumour burden was reduced in patients with high risk of TLS at baseline (n=34; 21.4%), with 94.1% of these patients being reclassified as having medium or low risk of TLS after three cycles of ibrutinib monotherapy. Furthermore, fewer patients had an indication for hospitalisation after three cycles of ibrutinib monotherapy (17.6%) than at baseline (39.6%).(66)

High-risk patients

Efficacy results from CAPTIVATE for the subgroup of patients with del17p and/or TP53 (n=27) are comparable to patients without del17p mutations, indicating I+V is likely to be effective in this patient population with a poor prognosis.

Primary endpoint: Depth of response per CR/CRi

The INV-assessed CR/CRi rate at primary analysis was 55.6% (95% CI: 36.8, 74.3) for high-risk patients, similar to patients without del17p.(66) A similar CR/CRi rate was observed for high-risk patients with extended follow-up (median 38.7 months) (55.6% [redacted]).(68, 69)

Secondary endpoint: PFS

The KM point estimate for INV-assessed PFS at 36 months was 80% (95% CI: 58%, 91%) for high-risk patients, similar to patients without del17p.(69)

Secondary endpoint: OS

The KM point estimate at 36 months was 96% (95% CI: 76%, 99%) for high-risk patients, similar to patients without del17p.(69)

B.2.6.2 GLOW (ITT)

Outcomes for the extended follow-up analysis (median 34.1 months follow-up) of the primary and secondary efficacy endpoints tested in the GLOW study are summarised in Table 16. Appendix M.2.2 includes a similar summary of clinical effectiveness based on the primary analysis (median 27.7 months follow-up).

Primary and key secondary endpoint (OS) results from both the primary and extended follow-up analyses of GLOW ITT are discussed in more detail in subsequent sections. Discussion of the other key secondary endpoints and additional secondary endpoints results is presented in Appendix M.2.4 and M.2.5, respectively.

Table 16 Summary of clinical effectiveness at a median follow-up of 34.1 months (GLOW; ITT extended follow-up analysis)

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
Primary Endpoint			
IRC-assessed PFS	Median, months (95% CI)	NE (NE, NE)	[redacted]
	Rate at 30 months, % (95% CI)	80.5% [redacted]	35.8% [redacted]
	HR (95% CI; p-value)	0.21 (0.13, 0.35; nominal p<0.0001[a])	
INV-assessed PFS (supplementary analysis)	Median, months (95% CI)	[redacted]	[redacted]
	Rate at 30 months, % (95% CI)	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Key Secondary Endpoints Tested in a Hierarchical Manner			
MRD negative rate in BM by NGS[b]	Rate, % (95% CI)	[redacted]	[redacted]
	Rate ratio (95% CI; p-value)	[redacted]	
IRC-assessed CR (CR/CRi) rate	Rate, % (95% CI)	[redacted]	[redacted]
	Rate ratio (95% CI; p-value)	[redacted]	
IRC-assessed ORR	Rate, % (95% CI)	[redacted]	[redacted]
	Rate ratio (95% CI, p-value)	[redacted]	
OS	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
	Rate at 30 months, % (95% CI)	[redacted]	[redacted]
	HR (95% CI, p-value)	0.76 (0.35, 1.64; [redacted]	
Rate of sustained haematological improvement	Rate of improvement in haemoglobin, %	[redacted]	[redacted]
	Rate ratio for improvement in haemoglobin (95% CI; p-value)	[redacted]	
	Rate of improvement in platelet count, %	[redacted]	[redacted]
	Rate ratio for improvement in platelet count (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in FACIT-Fatigue score[d]	Median, months (95% CI)	5.59 (3.81, 11.20)	3.75 (2.20, 5.75)
	HR (95% CI; p-value)	[redacted]	

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
Additional Secondary Endpoints			
DOR among patients with IRC-assessed PR or better	Median, months (95% CI)	[redacted]	[redacted]
TTNT	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in FACIT-Fatigue score[d]	Median, months	8.15 (3.98, 10.94)	14.03 (8.61, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EQ-5D-5L VAS score[d]	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EQ-5D-5L VAS score[d]	Median, months	8.34 (5.65, NE)	24.18 (11.27, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EQ-5D-5L Utility score[d]	Median, months	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EQ-5D-5L Utility score[d]	Median, months	14.29 (8.15, NE)	24.11 (8.34, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EORTC-QLQ-30 Global Health Status score[d]	Median, months	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EORTC QLQ-C30 Global Health Status score[d]	Median, months	14.95 (8.38, NE)	24.18 (13.86, NE)
	HR (95% CI; p-value)	[redacted]	
Reduction of TLS risk	Proportion with high risk of TLS at baseline reduced to medium/low,[e] n (%)	[redacted]	

BM = bone marrow; CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; del11q = 11q deletion; DOR = duration of response; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQoL-5 Dimension-5 Levels; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; O-Clb = obinutuzumab + chlorambucil; HR = hazard ratio; I+V = ibrutinib + venetoclax; IGHV = immunoglobulin heavy chain variable region; INV = investigator; IRC = Independent Review Committee; MRD = minimal residual disease; NE = not estimable; NGS = next generation sequencing; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient reported outcome; TLS = tumour lysis syndrome; TTNT = time to next treatment; VAS = visual analogue scale

[a] p-value is from a log-rank test stratified by IGHV mutational status and presence of del11q

[b] Results are presented based on the primary analysis; no additional assessment of MRD status by NGS was performed after the primary analysis

[c] p-value is from a Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status and presence of del11q

[d] Results are presented based on the primary analysis; no additional assessment of PRO measures was performed after the primary analysis

[e] After three cycles of ibrutinib monotherapy

[f] Results are presented based on the primary analysis; no analysis on reduction of TLS risk was conducted during extended follow-up

Source: Janssen Research & Development LLC [Data on File], 2021(70); Kater, 2022(67); Clinicaltrials.gov, 2022(75); Janssen Research & Development LLC [Data on File], 2021(77)

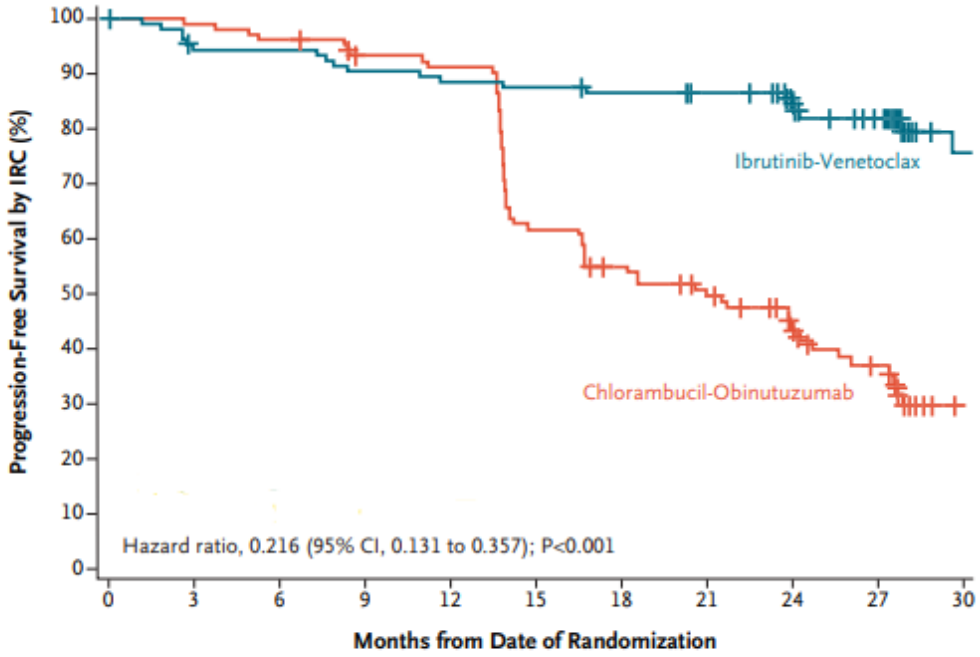
Primary endpoint: IRC-assessed PFS

PFS in GLOW was assessed by IRC (primary endpoint) and by the INV at both the primary analysis and the extended follow-up analysis.(67, 70) The primary endpoint was met. IRC- and INV-assessed PFS were consistent at both the primary and extended follow-up analyses.(70) Note that the economic analysis uses INV-assessed PFS based on the extended follow-up.

At the data cut-off for the primary analysis (26 February 2021) with a median follow-up of 27.7 months, patients treated with I+V had a significantly reduced risk of disease progression or death of 78% per IRC assessment compared to the O-Clb group (HR 0.22; 95% CI: 0.13, 0.36; nominal p<0.0001).(67, 70) At 24 months, the IRC-assessed PFS rate was 84.4% for the I+V group and 44.1% for the O-Clb group.(67) The KM plot from the primary analysis of IRC-assessed PFS is shown in Figure 11. The marked drop in the KM plot of PFS for O-Clb at approximately 15 months can be attributed to the protocol-specified mandatory imaging at fixed timepoints after randomisation and a period of 6 months without imaging prior to the evaluations at 15 months. Subgroup analyses of IRC-assessed PFS are presented in B.2.7Subgroup analysis.

As of the primary analysis, IRC-assessed PFS was consistent with INV-assessed PFS and all conducted sensitivity analyses.(67, 70) The KM plot of INV-assessed PFS as of the primary analysis is shown in Appendix M.2.3.

Figure 11 KM plot of IRC-assessed PFS (GLOW; ITT primary analysis)

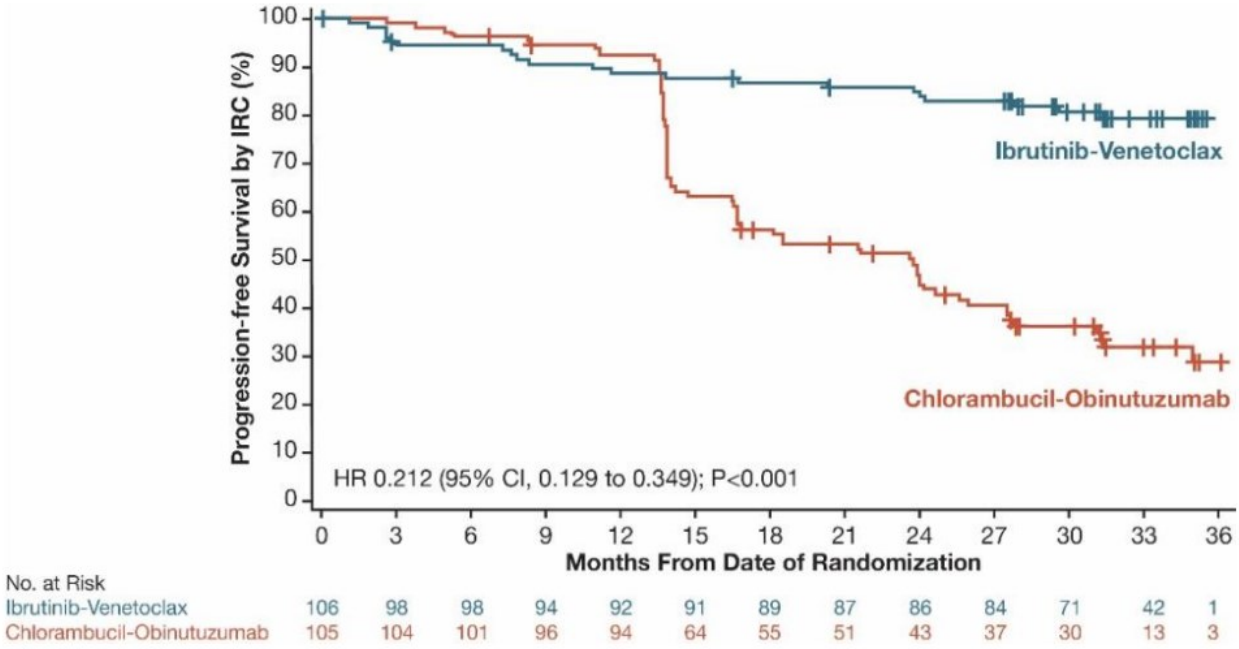


No. at Risk											
Ibrutinib-Venetoclax	106	98	98	94	92	91	89	87	71	59	20
Chlorambucil-Obinutuzumab	105	104	101	95	93	63	54	47	36	25	6

CI = confidence interval; IRC = Independent Review Committee; ITT = intent-to-treat; KM = Kaplan-Meier; PFS = progression-free survival
Source: Kater, 2022(67)

Extended follow-up (median 34.1 months) demonstrated that the difference in IRC-assessed PFS between the treatment groups was maintained long-term, with a significantly reduced risk of disease progression or death of 79% for the I+V group vs. the O-Clb group (HR 0.21; 95% CI: 0.13, 0.35; nominal p<0.0001; Figure 12).(67) Median IRC-assessed PFS was not reached for the I+V group and [redacted].(70) At 30 months, the IRC-assessed PFS rate was 80.5% for the I+V group and 35.8% for the O-Clb group.(67)

Figure 12 KM plot of IRC-assessed PFS (GLOW; ITT extended follow-up analysis)



CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; ITT = intent-to-treat; KM = Kaplan-Meier; PFS = progression-free survival
Source: Kater, 2022(67)

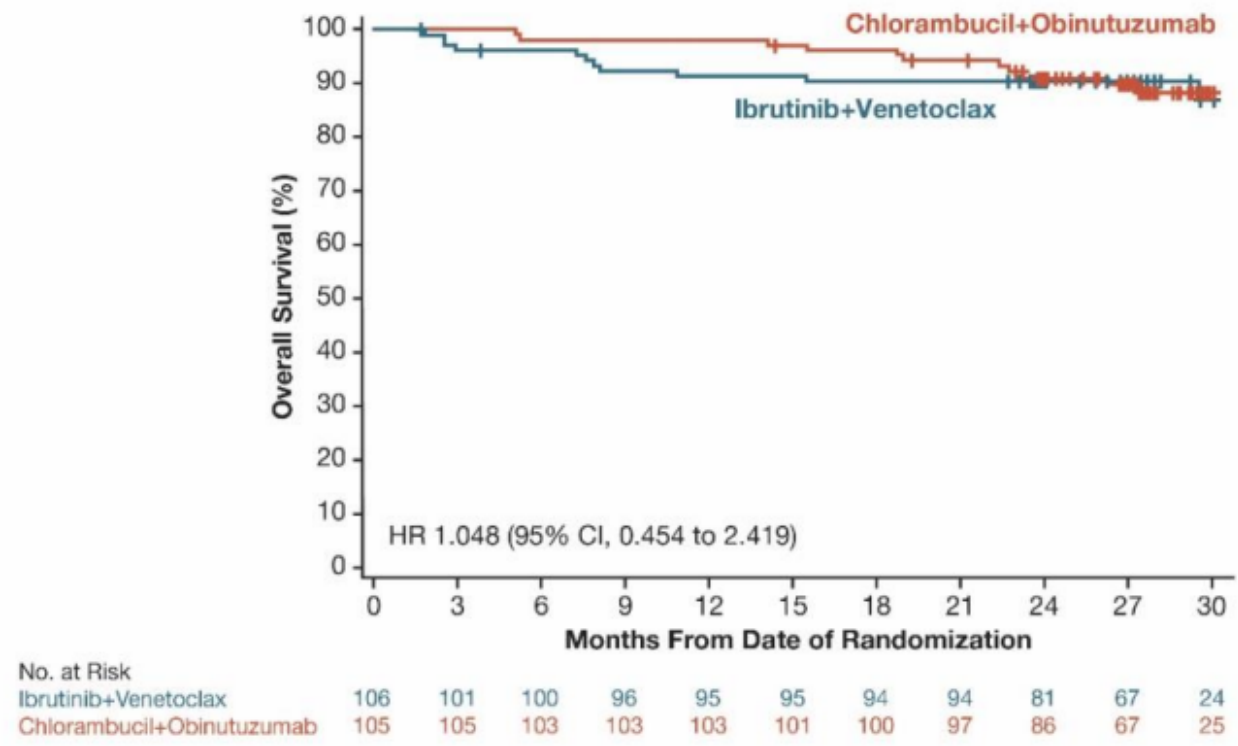
[redacted] The KM plot of INV-assessed PFS at extended follow-up (used in the economic analysis) is shown in Appendix M.2.3.

Key secondary endpoint: OS

At the primary analysis with a median follow-up of 27.7 months, there was no statistically significant difference in OS between the treatment groups (HR 1.05; 95% CI: 0.45, 2.42; nominal p=0.9121), with 11 deaths reported for the I+V group and 12 deaths reported for the O-Clb group. In the I+V group, four deaths occurred during ibrutinib lead

in, three during I+V treatment and four during follow-up. In the O-Clb group, two deaths occurred during treatment and the remaining 10 deaths occurred during follow-up.(67) The KM plot from the primary analysis of OS is shown in Figure 13.

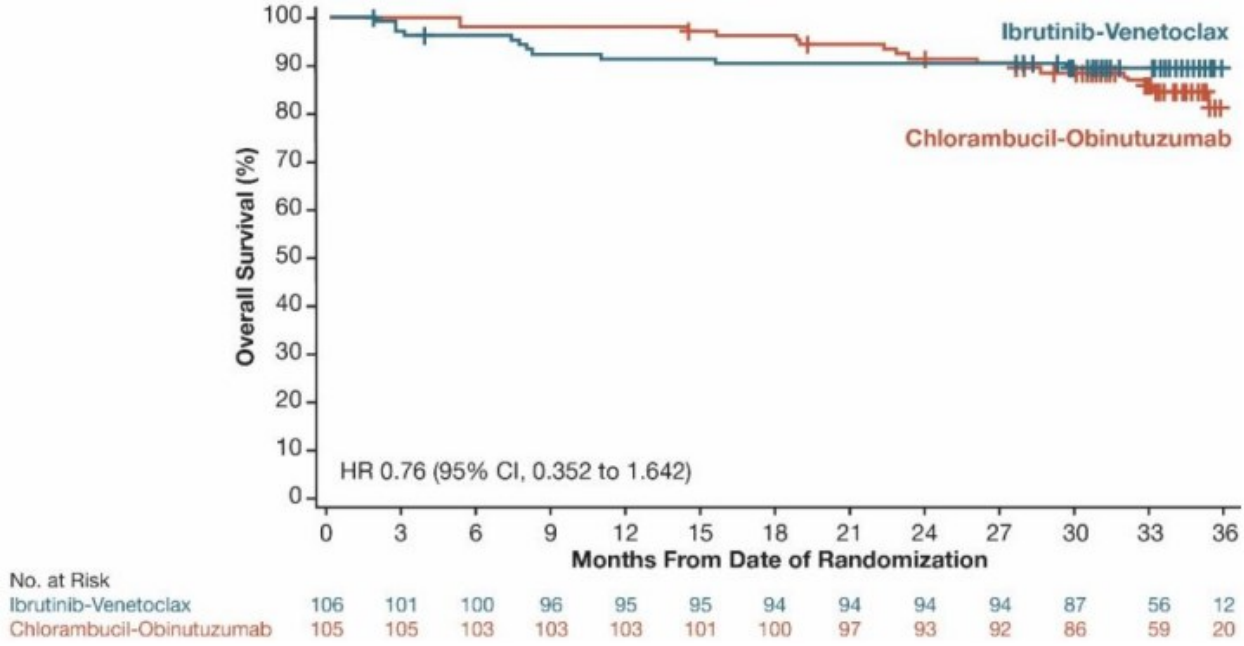
Figure 13 KM plot of OS (GLOW; ITT primary analysis)



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; OS = overall survival
Source: Kater, 2022(67)

At extended follow-up (median 34.1 months), four additional deaths occurred in the O-Clb group and the HR for OS in the I+V vs. O-Clb groups decreased to 0.76 (95% CI: 0.35, 1.64 [redacted]).(67, 70) Median OS was not reached in either treatment group.(70) [redacted] (Figure 14).(70) [redacted].(70) [redacted].(70)

Figure 14 KM plot of OS (GLOW; ITT extended follow-up analysis)



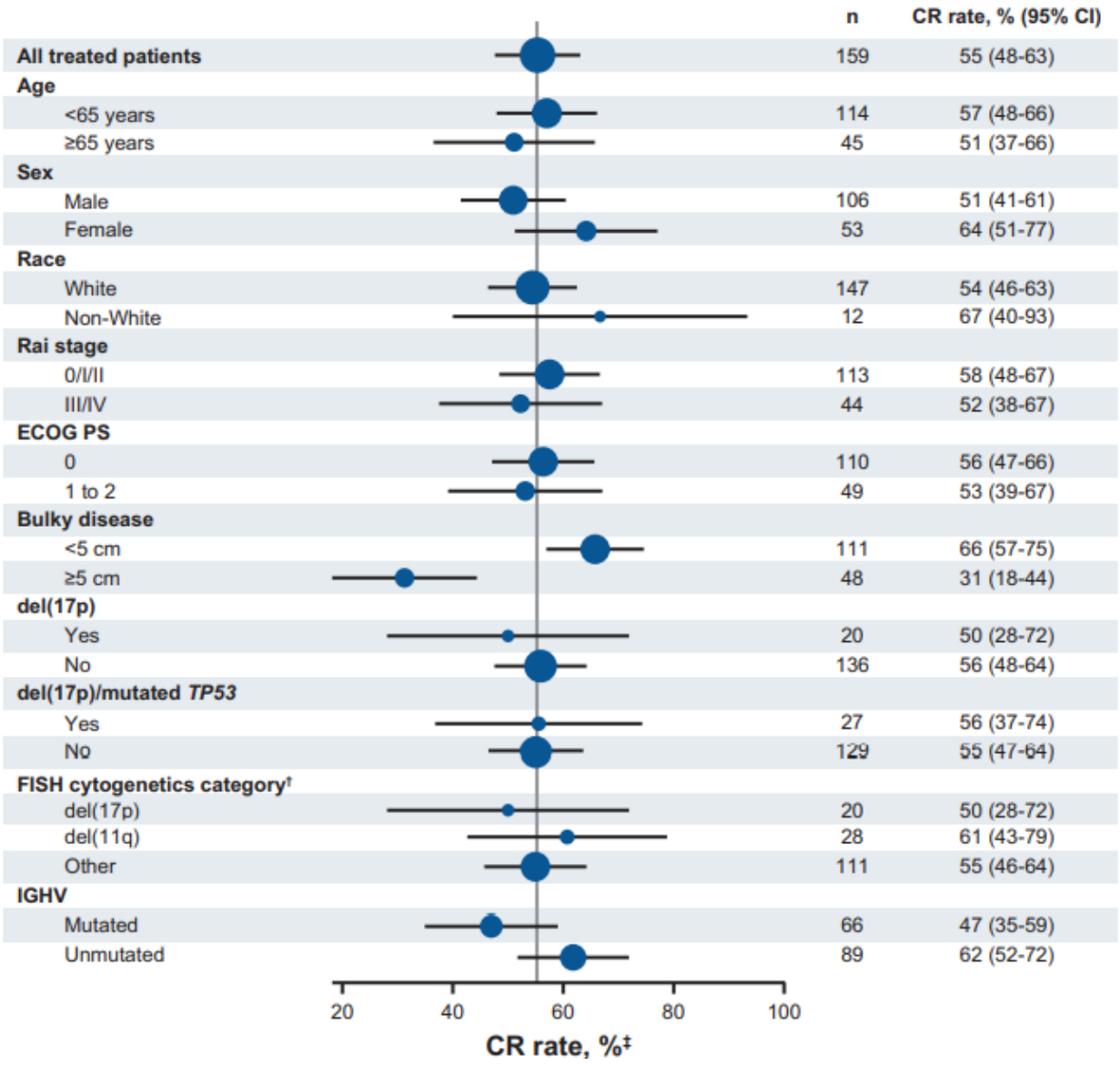
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; OS = overall survival
Source: Kater, 2022(67)

B.2.7 Subgroup analysis

B.2.7.1 CAPTIVATE (FD cohort)

As of the data cut-off for the primary analysis with a median follow-up of 27.9 months, the improvement in INV-assessed CR/CRi observed for all patients in the FD cohort was consistent across most pre-specified subgroups; a higher CR rate was observed in patients with unmutated vs. mutated IGHV (62% vs. 47%, respectively) and patients with bulky disease ≥5 cm vs. <5 cm (66% vs. 31%, respectively).(66) [redacted]

Figure 15 Forest plot of INV-assessed CR/CRi by pre-specified subgroups (CAPTIVATE; all treated population primary analysis)



CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; del11q = 11q deletion; del17p = 17p deletion; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; IGHV = immunoglobulin heavy chain variable; INV = investigator; TP53 = tumour protein p53
Source: Tam, 2022(66)

[redacted] (forest plot shown in Appendix E.1).(68) [redacted]

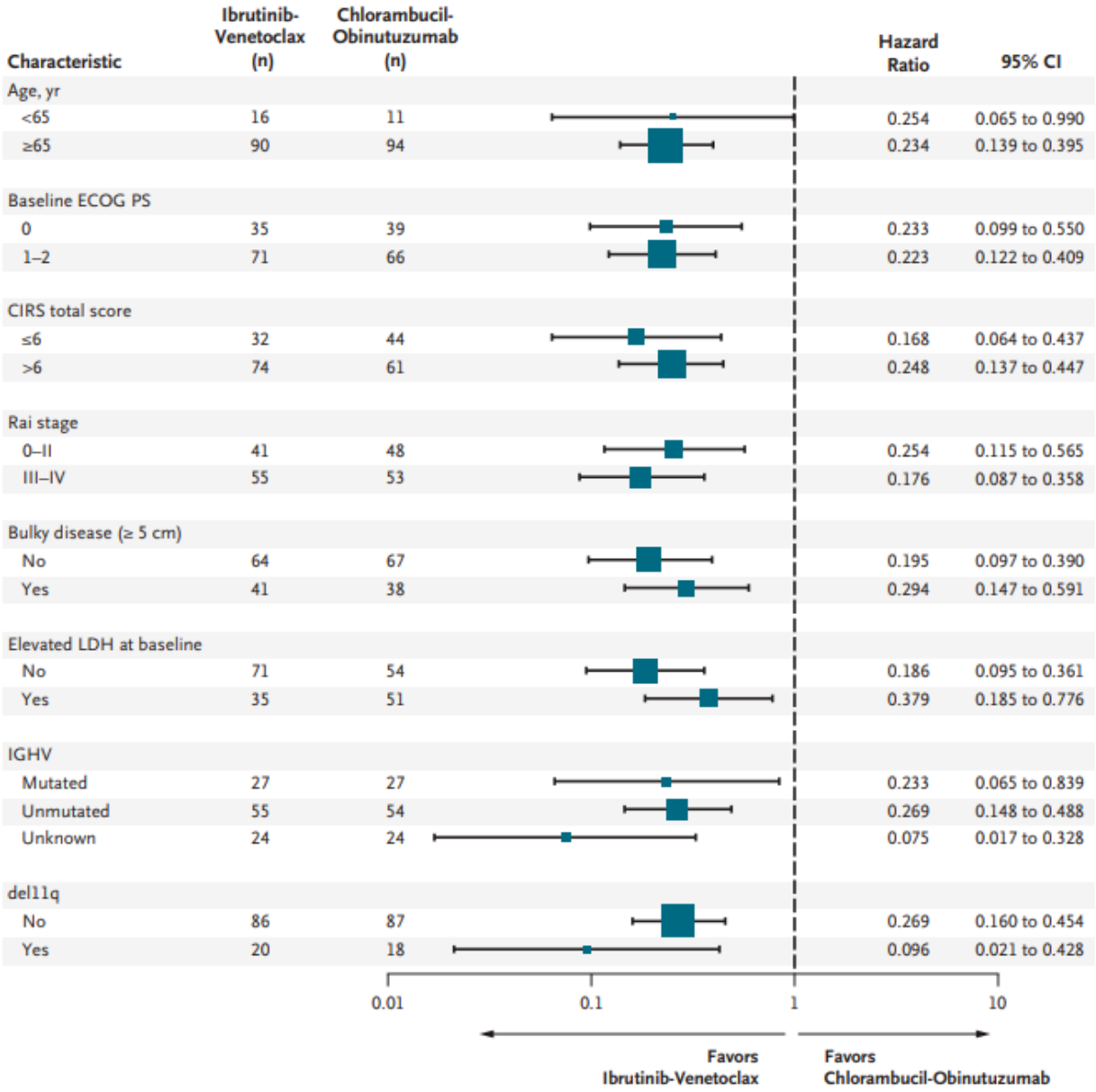
[redacted]

B.2.7.2 GLOW

At the data cut-off for the primary analysis (26 February 2021) with a median follow-up of 27.7 months, the improvement in IRC-assessed PFS with I+V treatment vs. O-Clb treatment was observed across pre-specified subgroups (XX XXX[redacted]

Figure 16), [redacted] (Appendix E.2).(67, 70) [redacted]

Figure 16 Forest plot of IRC-assessed PFS by pre-specified subgroups (GLOW; ITT primary analysis)



CI = confidence interval; CIRS = Cumulative Illness Rating Scale; del11q = 11q deletion; ECOG = Eastern Cooperative Oncology Group; IGHV = immunoglobulin heavy chain variable region; IRC = Independent Review Committee; ITT = intent-to-treat; LDH = lactic acid dehydrogenase; PFS = progression-free survival; PS = performance status
Source: Kater, 2022(67)

B.2.8 Meta-analysis

B.2.8.1 FCR-suitable population

Given the single-arm nature of the non-comparative FD cohort from the phase II clinical trial CAPTIVATE, it could not be considered for inclusion in a Bucher analysis or network meta-analysis (NMA) to generate comparative efficacy estimates vs. FCR, the key comparator. The NMA feasibility assessment in the FCR-suitable population is described in more detail in Appendix D.1.8.1.

B.2.8.2 FCR-unsuitable population

The feasibility of an NMA was assessed in the FCR-unsuitable population; however, the evidence suggested that an NMA would provide biased results. Therefore, it was concluded that pairwise comparisons using MAIC would be more appropriate to generate comparative efficacy estimates vs. VenO and acalabrutinib. The NMA feasibility assessment in the FCR-unsuitable population is described in more detail in Appendix D.1.8.1.

B.2.9 Indirect and mixed treatment comparisons

Relevant comparators for I+V include FCR in the FCR-suitable population, and O-Clb, VenO and acalabrutinib in the FCR-unsuitable population. In the high-risk population, the relevant comparators are VenO, acalabrutinib and ibrutinib.

GLOW provides head-to-head data for I+V vs. O-Clb, and ibrutinib efficacy is assumed equivalent to acalabrutinib in the high-risk population, based on the assumption made and accepted in TA689.

There are currently no data on direct comparisons of I+V with FCR, VenO or acalabrutinib, so ITCs are needed to derive comparative efficacy. The results for the ITC in the FCR-suitable population and the MAICs in the FCR-unsuitable population are described below. Appendix D.1.8.5 presents the strengths and limitations of these analyses.

B.2.9.1 ITC: I+V vs. FCR

Methods

The SLR identified several randomised trials of adult patients with previously untreated CLL eligible for fludarabine-based therapy and with FCR arms (namely, the CLL8, CLL10 and E1912 studies).

The CLL8 trial, an older FCR trial than the other identified trials, was ruled out because the FCR population differed in several ways from the CAPTIVATE I+V population (described in Appendix D.1.8.2). CLL10 was a newer FCR trial than CLL8 with a population that was more aligned with that of CAPTIVATE than CLL8. The E1912 (NCT02048813) trial studied FCR and ibrutinib + rituximab (I+R) treatment efficacy in adults with previously untreated CLL who were eligible for FCR.(78, 79) This trial was preferred to CLL8 and CLL10, since Janssen had access to individual patient data (IPD) from the E1912 48m median follow-up and was thus able to better align the CAPTIVATE and E1912 trial populations for the ITC analyses. Also, enrolled patients in E1912 and CAPTIVATE FD cohort were comparable:

- Diagnosed with CLL
- Treatment-naïve and required treatment per iwCLL 2008 criteria
- Aged between 18 and 70 years (both inclusive)
- Have an ECOG PS 0-2

A key difference in inclusion/exclusion criteria was that E1912 excluded patients with del17p while these patients were allowed in the CAPTIVATE study FD cohort. Therefore, only patients with no del17p in the CAPTIVATE FD cohort were included in the ITC analysis, and the analysis population was defined as adults with previously untreated CLL who would be eligible for fludarabine-based therapy, with no del17p, and who received at least one dose of study treatment. Based on data from CAPTIVATE and E1912, all treated patients without del17p consisted of 136 patients treated with I+V and 158 patients treated with FCR.

Inverse probability for treatment weighting (IPTW) with ATT weighting was used as the primary approach. The average treatment effect in the control population (ATC; i.e., adjusting to the FCR arm of E1912) and average treatment effect in the combined/overall population (ATO) were used as scenario analyses to explore robustness of the results in matching to different target populations.

The efficacy of I+V vs. FCR was analysed based on the following efficacy endpoints: PFS, OS, ORR and CR rate. For PFS, a weighted Cox proportional hazards model was used to derive a HR and its respective 95% CI. KM curves using IPTW were plotted. A weighted log-rank test was used to test the treatment effect between I+V and the comparator group. For binary outcomes (e.g., ORR, CR rate), a weighted logistic regression was used to derive an odds ratio (OR) with its respective 95% CI.

Results

After IPTW adjustment for all treated patients without del17p, applying ATT, ATC and ATO weighting, balance between the patient populations was generally achieved in all three approaches, except for some variables where missing values were key drivers of imbalances. Analyses excluding patients with missing covariate values achieved good model balance and were preferred for economic model analysis (see Appendix D.1.8.2).

Before adjustment, I+V demonstrated statistically significant PFS advantage over FCR for all treated patients without del17p, with [redacted], when excluding and including patients with missing covariate data, respectively. After adjustment using ATT for all treated patients without del17p excluding any patients with missing covariate data, the HR increased slightly for I+V vs FCR [redacted] In an analysis in which I+V was adjusted to the FCR arm of the E1912 trial (ATC approach), the I+V demonstrated statistically significant PFS advantage over FCR [redacted]

Results from the ATC and ATO analyses were consistent with the ATT analysis and demonstrated a statistically significant PFS advantage for I+V over FCR in all analyses

(see Appendix D.1.8.2). Sensitivity analyses excluding patients with known TP53 mutation was also carried out and are presented in Appendix D.1.8.2 along with other outcome results.

Table 17 I+V vs. FCR PFS results summary

	Unadjusted HR (95% CI) p-value	ATT HR (95% CI) p-value	ATC HR (95% CI) p-value
All treated patients without del17p excluding any with missing covariate values	[redacted]	[redacted]	[redacted]
All treated patients without del17p including any with missing covariate values	[redacted]	[redacted]	[redacted]

* ATC is used in the economic modelling, see B.3.3 Clinical parameters and variables
ATC = average treatment effect in the control population; ATT = average treatment effect in the treated population; CI = confidence interval; del17p = 17p deletion; HR = hazard ratio

B.2.9.2 Anchored MAIC: I+V vs. VenO

Methods

The SLR identified two randomised phase III studies of I+V or VenO in patients who would not be eligible for fludarabine-based therapies: the GLOW and CLL14 trials.

Given both trials had O-Clb as a comparator arm, anchored forms of ITC (Bucher and anchored MAIC) were considered. Although both studies used O-Clb as comparator treatment, there were notable differences in the inclusion/exclusion criteria as well as in patient baseline characteristics which were considered treatment-effect modifiers (TEMs) (see Appendix D.1.8.3). Given the differences in distribution of TEMs, anchored MAIC analyses were preferred over Bucher analyses since they aim to adjust for imbalances in TEMs and thus provide an unbiased estimate of treatment effect.

The longest follow-up for GLOW with 34.1-month median follow-up was selected for the MAIC to leverage the most mature data available for I+V. The 28.1-month follow-up from CLL14 was selected to closely align with the follow-up from GLOW. PFS was seen to be the most relevant endpoint given the maturity of data.

As a first step, the MAIC analysis excluded patients from the GLOW population who would not have been eligible for the CLL14 study based on the inclusion criteria differences identified, namely those without either CIRS score >6 or CrCl>70 mL/min. The remaining patients in the GLOW dataset were then weighted such that the mean values for relevant baseline parameters reflected the means, medians or proportions reported in CLL14.

Four characteristics (Age, ECOG PS, CIRS score, TP53 mutation status) were matched in the comparison of I+V vs. VenO. This approach was considered to offer an acceptable trade-off between matching characteristics and retaining effective sample size (N_{eff}), according to insights from an advisory board held with clinical and health economic experts from the UK in March 2022.(4)

There was evidence suggesting that the proportional hazards (PH) assumption was violated in GLOW and CLL14 for PFS. However, based on clinical expert feedback sought in May 2022, the use of a single HR approach (rather than the time-varying HR) was preferred as the base case analysis.(5) Nevertheless, scenario analyses were conducted by applying time-varying HR to investigate the impact on the results.

Results

Baseline characteristics of patients in GLOW before and after matching to CLL14 are presented in Appendix D.1.8.3. The exclusion step removed patients who did not have a CIRS >6 or did not have CrCl >70mL/min, in line with CLL14 inclusion criteria.

The results of the analyses for PFS (based on matching of the four top-ranked characteristics) are presented in Figure 17. Without adjusting for differences in baseline patient characteristics between the GLOW and CLL14 studies, the HR for PFS was [redacted]. After applying CLL14 exclusion criteria and matching of the four top-ranked characteristics, the HR for PFS was [redacted].

Scenario analyses were conducted and are presented in Appendix D.1.8.3.

Figure 17 PFS INV anchored MAIC results comparing I+V ([redacted] month follow-up) and VenO ([redacted] month follow-up)

CI = confidence interval; CLL = chronic lymphocytic leukaemia; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TP53 = tumour protein 53

B.2.9.3 Anchored MAIC: I+V vs. acalabrutinib

Methods

The SLR identified two randomised phase III studies of I+V or acalabrutinib in patients who would not be eligible for fludarabine-based therapies: the GLOW and ELEVATE-TN trials.

The GLOW and ELEVATE-TN studies both used O-Clb as comparator therapy. Therefore, an ITC using a common comparator was considered. Anchored MAIC analyses were preferred for similar reasons to those described above in B.2.9.2 Anchored MAIC: I+V vs. VenO.

The 34.1-month median follow-up from GLOW was used, and the 28.3-month follow-up from ELEVATE-TN was selected to closely align with the follow-up from GLOW. Four characteristics (Age, ECOG PS, CIRS score, TP53 mutation status) were matched in the comparison of I+V vs. acalabrutinib.

There was evidence suggesting that the PH assumption was violated in GLOW and CLL14 for PFS. However, based on clinical expert feedback sought in May 2022, the use of a single HR approach (rather than the time-varying HR) was preferred as the base case analysis.(5) Nevertheless, scenario analyses were conducted by applying time-varying HR to investigate the impact on the results.

Results

Baseline characteristics of patients in the GLOW trial before and after matching to the ELEVATE-TN study are presented in Appendix D.1.8.4. The exclusion step did not remove any patients as inclusion and exclusion criteria were generally aligned between the two studies; the only difference in exclusion criteria between the trials was that patients with del17p were excluded from GLOW, whereas these patients could be included in ELEVATE-TN. This difference could not be addressed owing to the unavailability of data specifically for those patients in the ELEVATE-TN study who did not have del17p (i.e., patients with del17p could not be removed from the dataset).

The results of the analyses for PFS (based on matching to the four characteristics listed above) are presented in Figure 18. Without adjusting for baseline patient characteristics between the GLOW and ELEVATE-TN studies, the HR for PFS was [redacted]. After applying the ELEVATE-TN exclusion criteria and matching of four characteristics, the HR for PFS was [redacted].

Scenario analyses were conducted and are presented in Appendix D.1.8.4.

Figure 18 PFS INV anchored MAIC results comparing I+V ([redacted] month follow-up) and acalabrutinib ([redacted] month follow-up)

CI = confidence interval; CIRS-G = Cumulative Illness Rating Scale-Geriatric; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TP53 = tumour protein 53

B.2.10 Adverse reactions

B.2.10.1 CAPTIVATE (FD cohort)

Overview

At the data cut-off for the primary analysis of the FD cohort with a median follow-up of 27.9 months, the median treatment duration was 13.8 months(66) and the median dose intensity was [redacted] for all study drugs. [redacted]

An overview of treatment-emergent AEs (TEAEs) reported in the FD cohort of the CAPTIVATE study is presented in Table 18. Overall, most patients (99.4%) experienced a TEAE, with grade ≥3 TEAEs and serious TEAEs occurring in 62.3% and 22.6% of patients, respectively.(74) TEAEs leading to treatment discontinuation were reported in 5.0% of patients (3.1% discontinued ibrutinib only; 0.63% discontinued venetoclax only; 1.3% discontinued I+V).(66) Dose reductions due to TEAEs occurred in 20.8% of patients (5.7% reduced ibrutinib only; 11.3% reduced venetoclax only; 3.8% reduced both).(66)

One fatal AE (sudden death) occurred in the FD cohort (during ibrutinib lead-in).(66) The event was determined to be possibly related to [redacted]

Table 18 Summary of TEAEs at a median follow-up of 27.9 months (CAPTIVATE; FD cohort safety population primary analysis)

TEAEs, n (%)	I+V (N=159)
Any TEAE	158 (99.4)
Any grade ≥3 TEAE	99 (62.3)
Any serious TEAE	36 (22.6)
TEAEs leading to discontinuation[a]	8 (5.0)
TEAEs leading to dose reduction[a]	33 (20.8)
Death	1 (0.6)

I+V = ibrutinib + venetoclax; TEAE = treatment-emergent adverse event
[a] Of any study drug
Source: ClinicalTrials.gov, 2022(74)

TEAEs by preferred term

An overview of common TEAEs (incidence ≥10% for any grade event or ≥2% for grade ≥3 events) reported in the FD cohort of the CAPTIVATE study is presented in Appendix F.1.1.

The most common TEAEs occurring in ≥20% of patients were diarrhoea (62.3%), nausea (42.8%), neutropenia (41.5%), arthralgia (33.3%), muscle spasms (29.6%), headache (25.2%), fatigue (24.5%), upper respiratory tract infection (23.3%), increased tendency to bruise (22.0%) and vomiting (22.0%).(68, 74)

The most common grade ≥3 TEAEs occurring in ≥5% of patients were neutropenia (32.7%), hypertension (5.7%) and neutrophil count decreased (5.0%).(66) The most common serious TEAEs occurring in ≥2% of patients were cellulitis (2.5%).(66)

Among TEAEs assessed by the INV to be related to treatment, TEAEs related to ibrutinib were reported in 92.5% of patients and TEAEs related to venetoclax were reported in 84.3% of patients.(74) The most common TEAEs related to ibrutinib occurring in ≥20% of patients included [redacted] The most common TEAEs related to venetoclax occurring in ≥20% of patients included [redacted]

AEs of clinical interest

In the CAPTIVATE study, major haemorrhage, including serious or grade ≥3 haemorrhagic AEs and any grade central nervous system (CNS) haemorrhage, was categorised as an adverse event of special interest (AESI).(73)

Treatment-emergent major haemorrhage events occurred in three (1.9%) patients and included cerebral haemorrhage, haemorrhagic cerebral infarction and retinal haemorrhage, of which none were fatal.(66) Treatment-emergent AESIs and select

events of potential clinical relevance to ibrutinib treatment are summarised in Appendix F.1.2.

Subsequent therapy

At the extended follow-up analysis, nine patients in the FD cohort had been retreated with single-agent ibrutinib therapy following disease progression, of which seven patients had a best response of PR and the remaining two patients were pending response evaluation.(66) [redacted]

B.2.10.2 GLOW

Safety data presented in this section are from the data cut-off for the primary analysis unless otherwise noted.

Overview

At the data cut-off for the primary analysis with a median follow-up of 27.7 months, all participants (N=211) in the GLOW study were off study treatment, of whom 77% had completed the I+V treatment course and 95% had completed the O-Clb treatment course. The median treatment duration (and AE reporting period) was substantially longer (2.7-fold difference) for the patients in the I+V group (13.8 months) vs. those in the O-Clb group (5.1 months).(67, 70) [redacted].(70)

An overview of TEAEs reported in the GLOW study is presented in Table 19. The overall incidence of TEAEs and grade ≥3 TEAEs was similar (<10% difference) between the groups during the treatment period (13.8 months for I+V and 5.1 months for O-Clb).(67, 70) The proportion of participants with serious TEAEs during the treatment period was higher in the I+V group vs. the O-Clb group.(67) [redacted]

[redacted].(70)

[redacted].(70) Treatment discontinuation of all study treatment due to AE occurred in 10.4% of I+V and 1.9% of O-Clb patients.(66, 67)

Nine participants died due to TEAEs, seven in the I+V group (including four during ibrutinib lead-in) and two in the O-Clb group. All four patients in the I+V group who died to due cardiac or sudden death had a CIRS score of ≥10 or an ECOG score of 2 and a medical history of diabetes, cardiovascular disease and/or hypertension. One death in each group (cardiac failure and pneumonia in the I+V group and pneumonia in the O-Clb group) considered by the INV to be related to study treatment.(67)

[redacted].(70)

Table 19 Summary of TEAEs at a median follow-up of 27.7 months (GLOW; safety population primary analysis)

TEAEs, n (%)	I+V (n=106)	O-Clb (n=105)
Any TEAE	105 (99.1)	99 (94.3)
Any grade ≥3 TEAE	80 (75.5)	73 (69.5)
Any serious TEAE	49 (46.2)	29 (27.6)
TEAEs leading to discontinuation[a]	[redacted]	[redacted]
TEAEs leading to dose reduction[a]	[redacted]	[redacted]
TEAEs leading to dose interruption[a]	[redacted]	[redacted]
Death	7 (6.6)	2 (1.9)

I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; TEAE = treatment-emergent adverse event
[a] Of any study drug
Source: Janssen Research & Development LLC [Data on File], 2021(70); Kater, 2022(67)

TEAEs by preferred term

An overview of common TEAEs (incidence ≥10% for any grade event or ≥2% grade ≥3 events) reported in the GLOW study is presented in Appendix F.2.1.

The most common TEAEs occurring in ≥20% of patients in the I+V group were diarrhoea (50.9%), neutropenia (including 'neutropenia' and 'neutrophil count decreased'; 41.5%) and nausea (26.4%) and in the O-Clb group were neutropenia (including 'neutropenia' and 'neutrophil count decreased'; 58.1%), infusion-related reaction (29.5%), thrombocytopenia (26.7%) and nausea (25.7%).(67) TEAEs that were more frequently reported in the I+V group vs. the O-Clb group (≥10% difference) were diarrhoea, rash, urinary tract infection, oedema peripheral, atrial fibrillation and hyperphosphatemia.(67) Conversely, TEAEs that were more frequently reported in the O-Clb group vs. the I+V group were neutropenia, thrombocytopenia, infusion-related reaction and pyrexia.(67, 70)

The most common grade ≥3 TEAEs occurring in ≥5% of participants in the I+V group were neutropenia (34.9%), diarrhoea (10.4%) hypertension (7.5%), atrial fibrillation (6.6%), pneumonia (6.6%), hyponatraemia (5.7%) and thrombocytopenia (5.7%) and in the O-Clb group were neutropenia (49.5%), thrombocytopenia (20.0%), pneumonia (5.7%) and TLS (5.7%).(67, 70) Grade ≥3 TEAEs that were more frequently reported in the I+V group vs. the O-Clb group (≥5% difference) were diarrhoea, hypertension, atrial fibrillation and hyponatraemia.(67) Conversely, grade ≥3 TEAEs that were more frequently reported in the O-Clb group vs. the I+V group vs. were neutropenia, thrombocytopenia and TLS.(67)

The most common serious TEAEs occurring in ≥2% of participants in the I+V group were atrial fibrillation (6.6%), pneumonia (5.7%), anaemia (2.8%), cardiac failure (2.8%) and diarrhoea (2.8%) and in the O-Clb group were pneumonia (5.7%), febrile neutropenia (2.9%) and infusion-related reaction (2.9%).(67) Serious TEAEs that were more frequently reported in the I+V group vs. the O-Clb group (≥2% difference) were atrial fibrillation (6.6% vs. 0%, respectively) and cardiac failure (2.8% vs. 0%).(67)

Conversely, serious TEAEs that were more frequently reported in the O-Clb group vs. the I+V group were infusion-related reaction and TLS (2.9% vs. 0% for both events).(67)

Overall and within the first 6 months of study treatment, the proportion of patients with TEAEs that were considered by the INV to be [redacted] Drug-related TEAEs that were more frequently reported in the I+V group vs. the O-Clb group (≥10% difference) were [redacted] (70)

AEs of clinical interest

[redacted].(70)

Treatment-emergent AESIs and select events of potential clinical relevance to ibrutinib treatment are summarised in Appendix F.2.2. [redacted].(70)

Subsequent therapy

Four patients in the I+V group required subsequent treatment due to CLL progression (n=2) or Richter's transformation (n=2). In the O-Clb group, 25 patients required subsequent treatment due to CLL progression and two patients required subsequent

treatment for Richter's transformation, of which 21 patients received single-agent ibrutinib and one patient received acalabrutinib.(67)

B.2.10.3 Safety summary

The safety observations from CAPTIVATE and GLOW demonstrated that the safety profile of FD I+V is consistent with the safety profiles of ibrutinib and venetoclax when administered as single agents. Together, results of CAPTIVATE and GLOW demonstrated an acceptable safety profile in patients with previously untreated CLL.(66, 67)

In the CAPTIVATE study, no new safety signals were identified for either study treatment.(66) TEAEs of any grade were reported in 99.4% of patients and grade ≥3 TEAEs were reported in 62.3% of patients.(74) Notable observations included a higher rate of diarrhoea and neutropenia compared to ibrutinib alone.(66) Most diarrhoea events were grade 1-2 in severity (62.3% any grade; 3.1% grade ≥3).(66) Rates of discontinuation due to AEs were <10% for both ibrutinib and venetoclax.(66)

In the GLOW study, the median treatment duration in the I+V group was 2.7-fold longer than the O-Clb group (13.8 vs. 5.1 months, respectively), which is important when comparing the incidence of TEAEs between groups. TEAEs of any grade and grade ≥3 TEAEs were reported in a similar proportion of patients in the I+V group (99.1% any grade; 75.5% grade ≥3) and the O-Clb group (94.3% any grade; 69.5% grade ≥3). A higher proportion of patients in the I+V group reported serious TEAEs compared to patients in the O-Clb group (46.2% vs. 27.6%, respectively). The incidence of TEAEs leading to discontinuation of any study drug was [redacted].(70) Treatment discontinuation of all study treatment due to AE occurred in 10.4% of I+V and 1.9% of O-Clb patients.(66, 67)

The safety observations for the extended follow-up were [redacted]

[redacted]

B.2.11 Ongoing studies

The CAPTIVATE and GLOW studies are both ongoing. [redacted]

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal interim findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The efficacy and safety of I+V in first-line CLL have been demonstrated in patients who are suitable for FCR (CAPTIVATE FD cohort) and in patients who are unsuitable for FCR (GLOW).(66, 70)

Efficacy

In the multi-centre, phase II CAPTIVATE study FD cohort, INV-assessed CR/CRi rate (primary endpoint) was 55.3% (95% CI: 47.6, 63.1) for all patients treated with FD I+V and 55.9% (95% CI: 47.5, 64.2) for patients without del17p at the primary analysis (median 27.9 months follow-up).(66) CR/CRi rates increased slightly to 57.2% (95% CI: 49.5, 64.9) and 58.1% (95% CI: 49.8, 66.4), respectively, with approximately 9 months of further follow-up.(68) CR/CRi rate across most pre-specified subgroups was higher than the study-assumed minimum rate of 37% and the rate observed with FCR in CLL10 (40%).(66, 76)

Secondary endpoint analyses from CAPTIVATE FD cohort supported the favourable CR rates, with the majority of CRs being durable for at least 12 months.(66, 68) INV-assessed ORR was 96.2% (95% CI: 93.3, 99.2) for all patients and 95.6% (95% CI:

92.1, 99.0) for patients without del17p at the primary analysis.(66) The overall proportion with MRD negativity in CAPTIVATE FD was ≥60% in the BM and ≥75% in the PB among all patients and patients without del17p at the primary analysis.(66) Response and MRD negative rates were maintained with extended follow-up, thereby attesting to the durability of efficacy in patients treated with FD I+V. Median [redacted] PFS or OS were not reached at the primary analysis or at extended follow-up. The KM point estimates for INV-assessed PFS and OS at 36 months were 88%, and 98%, respectively, among all patients.(69) The KM point estimates for INV-assessed PFS and OS at [redacted]

In a comparison of I+V and FCR in the FCR-suitable population, I+V demonstrated statistically significant PFS advantage over FCR in patients without del17p with no missing covariate values. After adjustment using ATT in the same population, a trend for better PFS with I+V over FCR was observed.

In the randomised, open-label, multi-centre, phase III GLOW study, primary analysis (median follow-up of 27.7 months) concluded that patients treated with I+V had a significantly reduced risk of disease progression or death of 78% per IRC assessment (HR 0.22; 95% CI: 0.13, 0.36; nominal p<0.0001) compared to patients treated with O-Clb.(67) Results from the primary analysis of PFS were consistent across pre-specified subgroups, including in [redacted] and in INV-assessed PFS (HR 0.21; 95%CI: 0.12-0.36).(67, 70) PFS benefit with I+V vs. O-Clb was maintained long-term with approximately 6 months of further follow-up [redacted] (67, 70)

The I+V group also had significantly higher overall MRD negative rate in BM by NGS [redacted] and significantly higher IRC-assessed CR/CRi [redacted] p<0.0001) compared to the O-Clb group at the primary analysis of GLOW. The [redacted] and MRD negative rates with I+V

remained high and the benefit vs. O-Clb was sustained throughout the first year after treatment completion.(70, 71) Furthermore, PFS rates 1 year after end of treatment of I+V were similar regardless of response and MRD status and better sustained than after treatment of O-Clb.(71) Lymph node responses were similar between I+V and O-Clb in patients with undetectable BM MRD but were better sustained with I+V in patients with detectable BM MRD.(71) Median OS was not reached in either treatment group with median 34.1 months follow-up, [redacted] Similar improvements in health status and HRQoL were observed in the [redacted]

Results of an MAIC show that the HRs for PFS and OS were in favour of I+V vs. VenO, before and after adjusting for baseline characteristics. HRs for PFS and OS from another MAIC were in favour of acalabrutinib before adjusting, but not statistically significant. After adjusting for baseline characteristics, PFS and OS outcomes were similar between I+V and acalabrutinib.

Safety

I+V demonstrated an acceptable safety profile in CAPTIVATE and GLOW, consistent with the known safety profiles of ibrutinib and venetoclax in other CLL regimens.(66, 67)

In the FCR-suitable population treated with FD I+V in CAPTIVATE, the rate of any grade TEAEs and grade ≥3 TEAEs was 99.4% and 62.3%, respectively, with rates of discontinuation due to AEs being <10% for both ibrutinib and venetoclax.(66, 74)

In the FCR-unsuitable population (GLOW), any grade TEAEs and grade ≥3 TEAEs were reported in a similar proportion of patients in the I+V group (99.1% any grade; 75.5% grade ≥3) and the O-Clb group (94.3% any grade; 69.5% grade ≥3), despite the exposure time for O-Clb being shorter (2.7-fold difference); the incidence of TEAEs leading to discontinuation of any study drug was [redacted] and treatment discontinuation of all study

treatment due to AE occurred in 10.4% of I+V and 1.9% of O-Clb patients.(67, 70) Grade ≥3 neutropenia and thrombocytopenia, common AEs associated with CIT,(80-82) were observed at higher rates with O-Clb than I+V in GLOW.(67)

No cases of TLS with I+V treatment were reported in the CAPTIVATE or GLOW studies.(66, 67)

B.2.12.2 Strengths and limitations in context to UK clinical practice

Strengths

Internal validity of CAPTIVATE and GLOW

I+V has been extensively studied in two international, multi-centre RCTs investigating its efficacy and safety in previously untreated patients with CLL considered suitable for FCR (CAPTIVATE study) and considered unsuitable for FCR (GLOW study). Both studies were considered to be of high quality.

The results were considered to be at low risk of bias because:

- Investigator-assessed outcomes were further assessed and confirmed by an IRC
  - Assessment of the primary outcome in CAPTIVATE FD cohort, CR/CRi rate, was consistent with [redacted]
  - The primary outcome in GLOW, IRC-assessed PFS, was consistent with INV-assessed PFS at the primary analysis [redacted].(70)
- All randomised patients in GLOW were included in the efficacy analysis, thus preserving randomisation.(67)

External validity of CAPTIVATE and GLOW

Results from CAPTIVATE and GLOW can be generalised to the UK population, considering over 90% of patients were Caucasian in both studies, and GLOW included eight UK study sites.(67, 74)

- Patients included in the CAPTIVATE study FD cohort appropriately represented the population of patients with CLL considered suitable for more intense treatment with FCR, with most patients being <65 years of age and more fit with CrCl ≥60 mL/min.(66); 27% of patients with CLL are diagnosed below 65 years in England.(15)
- Patients included in the GLOW trial appropriately represented the population of CLL patients who are unsuitable for fludarabine-based CIT but are likely to tolerate less-intense treatment with O-Clb, based on age (≥65 years) or CIRS score >6 and CrCl <70 mL/min. The median patient age in GLOW was 71.0 years, which is similar to the median age of CLL diagnosis reported in England (72 years).(15, 67)
- Both studies assessed a range of efficacy outcomes considered relevant to patients and clinicians (PFS, CR/CRi, OS, MRD, ORR and DOR); GLOW also included EQ-5D-5L and EORTC QLQ-C30 assessments to evaluate HRQoL.(68, 70)

Limitations

While substantial and clinically meaningful benefits have been demonstrated with I+V in patients with previously untreated CLL in the CAPTIVATE and GLOW studies, certain potential limitations should be considered.

Immature data

In CAPTIVATE, median PFS and OS were not reached at primary analysis or at extended follow-up.(66, 69)

In GLOW, while the IRC-assessed PFS rate at 24 months was significantly higher in the I+V group than in the O-Clb group (84.4% vs. 44.1%; p<0.0001), median PFS was not

reached in the I+V group.(67) Moreover, the IRC-assessed ORR was not significantly different between treatment groups ([redacted]), though significant differences were observed in IRC-assessed CR rate and MRD negative rate at the primary analysis (both p<0.0001). Median OS was also not reached in the I+V or O-Clb group, and OS was comparable between treatment groups at the primary analysis (HR 1.05; 95% CI: 0.45, 2.42; nominal p=0.9121).(67, 70)

Further follow-up is required to capture the full PFS benefit of I+V in patients with previously untreated CLL and to reduce uncertainty about whether PFS benefit translates to OS benefit. PFS benefits with first-line treatment of CLL have translated to OS benefits with longer follow-up (>5 years) for several treatments (including O-Clb, I+R and ibrutinib monotherapy).(6, 83, 84)

Indirect comparison

While the INV-assessed CR/CRi rate in patients treated with I+V in CAPTIVATE was higher than the CR/CRi rate of patients treated with FCR in CLL10 (>55% vs. 40%), no clinical trials have directly compared the efficacy of first-line I+V with FCR.(66, 76)

There are no results currently available from any ongoing clinical trials directly comparing the efficacy of first-line I+V with VenO and acalabrutinib in the previously untreated FCR-unsuitable CLL population.

In the FCR-suitable population, a patient-level data ITC was conducted to inform efficacy of I+V vs. FCR. This approach has high internal validity, given that it uses individual patient data to match patients and make the patient populations more comparable. In the FCR-unsuitable population, anchored MAICs were conducted to inform comparative efficacy of I+V vs. VenO and acalabrutinib. Anchored comparisons are preferred over unanchored comparisons, and this approach was validated by clinical experts.

Efficacy estimation in high-risk patients

Efficacy results from CAPTIVATE for the subgroup of patients with del17p and/or TP53 mutation indicates that I+V is likely to be effective in this patient population with a poor prognosis. However, there is a general paucity of evidence in the high-risk population considering:

- the low number of patients with these characteristics (del17p/TP53 mutation) in the CAPTIVATE and GLOW trials(66, 67)
- the low number of patients in this population contributing to efficacy data and lack of published OS data for this subgroup for other comparators such as VenO (CLL14) and acalabrutinib (ELEVATE-TN)(85, 86)

Therefore, the clinical efficacy of I+V in high-risk patients was assumed equivalent to FCR-unsuitable patients. This assumption was used and accepted in TA689,(2) where clinical experts explained that it was reasonable to assume a similar treatment effect of acalabrutinib for the populations with untreated CLL whether or not they had high-risk CLL. This assumption was further validated by clinical expert opinion in May 2022,(5) but results should still be interpreted with caution.

B.2.13 Conclusion

I+V is a combination of two targeted agents; the complementary effects of ibrutinib and venetoclax lead to more effective clearance of CLL from the blood, BM and lymph node compartments, as well as direct killing of CLL cells. This synergistic action may result in greater long-term PFS benefits compared with currently available FD treatment regimens; PFS with current follow-up was not dependent on MRD status with I+V.(66, 71)

Patients and physicians in the UK desire effective, targeted regimens that induce CRs and reduce relapses in the broadest population of patients with CLL without continuous administration and with an acceptable safety profile. Patients with previously untreated CLL lack a convenient all-oral, FD, chemotherapy-free treatment regimen that does not induce substantial treatment-related toxicities. In particular, younger patients who are

suitable for FCR would benefit from treatment options that can be administered at home, thereby reducing disruption to daily life, e.g., in terms of work commitments and childcare.

I+V addresses the unmet need in CLL by being the first all-oral, once daily, chemotherapy-free, FD regimen that patients can take at home, without the need for infusion-based hospital treatments. The unique dual-oral posology may be preferred by some patients and has positive resource implications for the NHS, which is currently recovering from a global pandemic, by helping to alleviate the backlog of patients waiting to be treated. Furthermore, patients and the clinical community will value the opportunity to administer a combination of two effective agents upfront to reduce the resource burden associated with relapse.(17, 46-48)

I+V prolonged PFS with deep and durable response rates in previously untreated patients with CLL in CAPTIVATE and GLOW.(66, 67) The safety profile of I+V demonstrated in CAPTIVATE and GLOW was consistent with the known safety profiles of ibrutinib and venetoclax in other CLL regimens.(66, 67) With a 3-cycle lead-in, ibrutinib allowed for an initial reduction in tumour burden, decreasing the number of patients at higher risk of TLS.(66, 67)

In addition to the clinical benefits, I+V helps patients avoid a life of medicalisation by reducing hospital appointments and offering patients a ‘treatment-free holiday’ between finishing the FD treatment and beginning second line treatment upon progression.

Reactions to the concept of an all-oral FD treatment were generally positive in an advisory board conducted with three trustees/patients from the CLL Support Association. Respondents highlighted the following as benefits associated with an all-oral treatment: reduced “stress of coming into a clinical setting when your immune system is compromised”, “freedom to go on vacation, peace of mind and better QoL”. Respondents also described several advantages of FD treatment, such as being able to “live normally and plan things” and to regain “some sort of control” during treatment-free periods.(18)

B.3 Cost effectiveness

Model Overview

- A *de novo* semi-Markov four health state model was created to identify the cost-effectiveness of I+V in comparison to:
    - FCR in the FCR-suitable population
    - O-Clb, VenO and acalabrutinib in the FCR-unsuitable population
    - VenO, acalabrutinib and ibrutinib in the high-risk population
- State occupancy was modelled in 28-day cycles over a lifetime horizon (up to 40-year and 30-year time horizons for FCR-suitable and FCR-unsuitable/high-risk populations, respectively) using data from key clinical trials with the longest available follow-up to inform first-line PFS, second-line PFS, mortality during PFS and post second-line survival.
- In FCR-suitable patients, the E1912 trial with 70 months of follow-up data was used to inform long-term PFS in the FCR arm, and I+V comparative efficacy was based on a propensity score comparison using IPD for CAPTIVATE and E1912 (B.2.9 Indirect and mixed treatment comparisons).
- In FCR-unsuitable patients, data from GLOW was used to model I+V and O-Clb independently. Comparative efficacy data for I+V vs. VenO and acalabrutinib was generated from anchored MAICs, after adjusting for differences in trial population characteristics (GLOW, CLL14 and ELEVATE-TN).
- Due to limited evidence in the high-risk population, inputs for this group were assumed to be equivalent to the FCR-unsuitable population, based on the assumption accepted in TA689 and further clinical validation. Ibrutinib efficacy was assumed to be equivalent to acalabrutinib, based on the assumption from TA689.
- Costs incorporated in the model included drug acquisition and administration for first- and second-line treatment, AE management, disease management and terminal care. Utility was based on the GLOW trial, accounting for age adjustments, and previous NICE appraisals.

Results

- The output of the model demonstrates that I+V is cost-effective in all three subpopulations:
    - In the FCR-suitable population, the incremental cost-effectiveness ratio (ICER) is £8,277. Results are driven by comparatively longer PFS and OS with I+V vs. FCR, and subsequent offsets in costs from delaying subsequent treatments.
    - In the FCR-unsuitable population, I+V dominates VenO and O-Clb (i.e., I+V is less costly and more effective). Compared with acalabrutinib, I+V is less costly and less effective (southwest quadrant) at an ICER of £1,546,602 per quality-adjusted life year (QALY) forgone.
    - In the high-risk population, I+V dominates VenO (i.e., I+V is less costly and more effective). Compared with acalabrutinib and ibrutinib, the ICERs are £1,546,602 and £675,793per QALY forgone, respectively (falling in the southwest quadrant).
    - Note that because I+V is a 'southwest quadrant' technology with respect to acalabrutinib and ibrutinib, this means higher ICERs make I+V more cost-effective – ICERs in the range demonstrated above are far in excess of any threshold NICE has historically used.

- These results were consistent in all the scenario and sensitivity analyses conducted.
- Validation of model projections involved comparisons against long-term data (70 months for E1912, 65 months for RESONATE and 88.5 months for RESONATE-2) and elicitation of clinical expert opinion

Benefits not captured in the QALY calculation

- I+V offers benefits not captured in the QALY by its potential to reduce medicalisation in all three populations compared to current standard of care. In addition to the clinical benefits, I+V helps patients avoid a life of medicalisation by reducing hospital appointments and offering patients a 'treatment-free holiday' between finishing the FD treatment and beginning second line treatment upon progression.
- The unique dual-oral posology of I+V has positive resource implications for the NHS, which is currently recovering from a global pandemic, by helping to alleviate the back-log of patients waiting to be treated.

Conclusions

- I+V is an effective use of NHS resources in all subpopulations. The clinical evidence and economic analysis highlight that I+V would address significant unmet need for previously untreated CLL patients.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify studies, published between 2011 and 2022, reporting economic outcome data for patients with previously untreated CLL.

The review identified three cost and resource use studies and 38 economic evaluation publications in the FCR-suitable and -unsuitable patients. Of the 38 cost-effectiveness analyses, 19 publications reported analyses which were conducted using a UK healthcare perspective. Fifteen out of 19 publications evaluated a treatment of interest in the UK; nine were UK HTA submissions, whereas the other six were models with a UK perspective published in journal articles.

Five cost-effectiveness analyses were identified which carried out analysis for patients with del17p/TP53 mutation. All five publications were previously published HTA submissions from a UK perspective.

Studies were only extracted if they included I+V or comparators of interest (FCR, O-Clb, VenO, acalabrutinib, ibrutinib monotherapy) in the first-line setting from a UK

perspective. Full details of the SLR search strategy, methodology and results are presented in Appendices G and I.

B.3.2 Economic analysis

A *de novo* economic model was developed in Microsoft Excel© to estimate the ICER of I+V vs. the corresponding first-line comparators in the FCR-suitable, FCR-unsuitable and high-risk populations. Features of the current economic analysis are summarised and compared to the NICE appraisals in previously untreated CLL for VenO (TA663) and acalabrutinib (TA689) in Table 20.

Table 20 Key characteristics of the economic analyses

Parameter	Recent previous appraisals		Current appraisal		
	TA663(1)	TA689(2)	Chosen value		Justification
Population (previously untreated CLL)	FCR-unsuitable and high-risk patients (Note that FCR-suitable was added later in the evaluation process)	FCR-unsuitable and high-risk patients	FCR-unsuitable† and high-risk patients	FCR-suitable† patients	Aligned with the NICE scope and anticipated license for I+V; includes patients enrolled in CAPTIVATE and GLOW for the FCR-suitable and -unsuitable populations, respectively
Intervention	VenO	Acalabrutinib	I+V		Aligned with NICE scope
Comparator: FCR-suitable	NA	NA	NA	FCR	Aligned with current clinical care pathway, BSH guidelines and NICE scope (details for comparator rationale discussed in B.1.1 Decision problem)
Comparator: FCR-unsuitable	O-Clb	O-Clb	O-Clb Acalabrutinib VenO	NA	
Comparator: High-risk population	Ibrutinib	Ibrutinib	VenO Acalabrutinib Ibrutinib	NA	
Date published	2020	2021	NA		NA
Model structure	Partitioned survival (3-health state)	Semi-Markov (3-health state)	Semi-Markov (4-health state)		• Enables long-term projection of OS using data from external trials, reducing uncertainty in long-term survival extrapolations • Considers efficacy and costs in subsequent lines • Accepted in prior HTA submissions for anti-cancer treatments in CLL (TA487, TA343, TA359, TA689)(2, 58, 62, 87) • See B.3.13.1 Validation of cost-effectiveness analysis for more detailed justification
Time horizon	30 years	30 years	30 years	40 years	• Captures long-term clinical and economic impacts of CLL while limiting uncertainty in projecting health outcomes beyond trial periods

Parameter	Recent previous appraisals		Current appraisal		
	TA663(1)	TA689(2)	Chosen value		Justification
					• FCR-suitable population (median age 58 years)(83) was younger than the FCR-unsuitable population (median age 71 years)(70) requiring a longer time horizon
Starting age	71.1 years (non-del17p/TP53) 69.6 years (del17p/TP53)	70 years	71 years (FCR-unsuitable and high-risk);	58 years	Median age of populations from key FCR-suitable trial (83) and GLOW ITT
Cycle length	4 weeks	4 weeks	4 weeks		All treatments of interest follow a 4-week treatment cycle
Half cycle correction	Included	Included	All costs and outcomes are half-cycle corrected, except for the treatment acquisition costs and administration costs that are assumed to occur at the start of each model cycle		Consistent with NICE requirements.
Analysis type	Cost-effectiveness	Cost-effectiveness for FCR-unsuitable Cost minimisation for high-risk	Cost-effectiveness		Comparators with varying efficacy except equivalent efficacy assumed between acalabrutinib and ibrutinib in high-risk patients
Clinical effectiveness: Pre-progression	PFS and TTNT based on CLL14 ITT High-risk based on del17p/TP53 subgroup in CLL14 trial (covariate in fits)	Time to progression and time to death based on ELEVATE-TN	FCR-unsuitable: PFS and pre-progression mortality derived from GLOW trial for I+V and O-Clb; MAIC informs PFS vs. I+V for VenO and acalabrutinib	PFS reference based on FCR from E1912. I+V was informed via an ITC vs. FCR from E1912	• Leverages I+V trial data • PFS is the most reported outcome across trials of interest allowing for comparisons across trials • Second-line PFS is used to inform time on subsequent treatment as in prior TAs (TA663 and TA689)(1, 2) • Mortality in 1L and 2L PFS is used to determine patients with a death event rather than a progression event for the

Parameter	Recent previous appraisals		Current appraisal		
	TA663(1)	TA689(2)	Chosen value		Justification
			High-risk: Assumed equivalent to FCR-unsuitable patients		composite endpoint of PFS and determines those eligible for the 2L PFS and PPS health states
Clinical effectiveness: Post-progression	PPS based on CLL14 ITT	PPS based on RESONATE (1-2 prior lines; preferred by ERG) and MURANO	PPS states based on RESONATE subgroup of 1-2 prior lines		RESONATE subgroup of 1-2 prior lines represents survival in a population treated with BTKi in 2L. Approach was accepted in previous NICE appraisal TA689(2)
Extrapolations	PFS independently extrapolated; OS assumed to be the same across the two treatment arms Naïve comparisons of ibrutinib and VenO for del17p/TP53 (ibrutinib informed by Mato et al. 2018) (88)	PFS independently extrapolated Ibrutinib monotherapy is assumed to have the same efficacy as acalabrutinib monotherapy in del17p/TP53	I+V and O-Clb PFS independently extrapolated; HRs vs. I+V for VenO and acalabrutinib monotherapy from an anchored MAIC In del17p/TP53 Ibrutinib monotherapy is assumed to have the same efficacy as acalabrutinib monotherapy	FCR arm independently fitted; HR applied based on propensity score analysis of I+V vs. FCR (E1912)	• Independent extrapolations were chosen in FCR-unsuitable as PH and AFT assumptions were violated in GLOW. • Propensity score analysis was chosen in FCR-suitable given that PLD was available for both the E1912 and CAPTIVATE trials
Subsequent treatment options, duration and treatment-free interval (delay between progression in first-line and	Ibrutinib and VenR Second-line treatment duration based on RESONATE TFI calculated using PFS and TTNT	Ibrutinib and VenR TFI specified as a number of cycles between disease progression and starting subsequent treatment; ERG	Ibrutinib, acalabrutinib and VenR Subsequent treatment duration is informed by the ibrutinib PFS from RESONATE final analysis (median 65-month follow-up) subgroup of 1-2 prior lines. The treatment duration for ibrutinib		Subsequent treatment duration is explicitly and transparently reflected as opposed to assuming that patients receive subsequent treatment for a fixed number of cycles or lifetime.

Parameter	Recent previous appraisals		Current appraisal		
	TA663(1)	TA689(2)	Chosen value		Justification
second-line treatment initiation)		base case used 14 cycles	and acalabrutinib is until progression and up to 24 months for VenR TFI is assumed to be 14 cycles based on clinical and health economic expert validation(4), and based on ERG base case in TA689(2)		
Utility source	PF and PD states sourced from TA for O-Clb for untreated CLL (TA343) Disutilities associated with AEs were sourced from previous NICE submissions	PF state: Based on EQ-5D data collected in the ELEVATE-TN trial PD state: Alternative values sourced from published literature and previous CLL submissions Disutilities associated with AEs were sourced from published literature and previous CLL submissions	PF state: Based on EQ-5D data collected in the GLOW trial PD state: Alternative values sourced from published literature and previous CLL submissions Disutilities associated with AEs were sourced from previous CLL submissions	PF state: GLOW utilities further age adjusted to reflect younger population PD state and disutility: same as FCR-unsuitable population	Consistent with utility in other trials. Trial based utility consistent with NICE manual; EQ-5D-3L is the preferred measure of HRQoL in adults, according to the NICE reference case. Given that CAPTIVATE and other first-line trials of the FCR-suitable population did not collect any PROs for utility, the same first-line utility used for the FCR-unsuitable/ high-risk populations was also used for the FCR-suitable population, with adjustment to reflect the lower starting age of the FCR-suitable patients. Age adjustment was applied per the NICE manual.
Were health effects measured in QALYs; if not, what was used?	QALYs				NICE reference case
Discount rate for costs and outcomes	3.5%				NICE reference case
Perspective	NHS/PSS				NICE reference case

Parameter	Recent previous appraisals		Current appraisal	
	TA663(1)	TA689(2)	Chosen value	Justification
Sources of costs	MIMS, BNF and NHS reference costs			NICE reference case

1L = first line; 2L = second line; AE = adverse event; AFT = accelerated failure time; BNF = British National Formulary; BSH = British Society for Haematology; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukaemia; del17p = 17p deletion; ERG = Evidence Review Group; FCR = fludarabine, cyclophosphamide, rituximab; HR = hazard ratio; HTA = health technology assessment; ITC = indirect treatment comparison; ITT = intent to treat; I+V = ibrutinib + venetoclax; MAIC = matching-adjusted indirect comparison; MIMS = Monthly Index of Medical Specialties; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; O-Clb = obinutuzumab + chlorambucil; OS = overall survival; PD = progressive disease; PF = progression-free; PFS = progression-free survival; PH = proportional hazards; PLD = patient-level data; PPS = post-progression survival; PRO = patient-reported outcome; PSS = Personal Social Services; QALY = quality-adjusted life year; TA = technology appraisal; TFI = treatment-free interval; TP53 = tumour protein 53; TTNT = time to next treatment; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab

† Excludes patients with del17p mutation

B.3.2.1 Patient population

The model considered three separate patient populations with previously untreated CLL, as follows:

- FCR-suitable patients: patients with no del17p mutation, with CIRS ≤6, CrCl ≥70 mL/min and ECOG PS <2
- FCR-unsuitable patients: patients with no del17p mutation, with CIRS >6 and/or CrCl <70 mL/min who are ≥65 years old or 18-64 years old with comorbidity
- High-risk patients: Patients with del17p/TP53 mutation

The three populations considered in the evidence submission are defined in Table 21.

Table 21 Populations considered in the submission

Population	Rationale
FCR-suitable and FCR-unsuitable populations are described as “no del17p”, rather than “no del17p/TP53” because the cohorts from the respective trials, used in the economic model, include some patients with TP53 mutation. The implications of removing those patients from the datasets are outlined below.	
Population 1: FCR-suitable patients Patients with no del17p mutation, with CIRS ≤6, CrCl ≥70 mL/min and ECOG PS <2	This population best reflects the cohort of the trial CAPTIVATE. The FD cohort of CAPTIVATE, used in the economic model, has no del17p patients but includes some patients with TP53 mutation. Removal of patients with TP53 mutation from the dataset is possible, but comes at the cost of the following consideration: • The E1912 trial is used as a reference curve for FCR and included TP53-mutated patients (but excluded del17p). Only aggregate data is available for the latest datacut of E1912 (70-month follow-up), so TP53-mutated patients cannot be removed; therefore, it is appropriate to leave these patients in for I+V from CAPTIVATE FD as well. Exclusion of TP53-mutated patients was not found to substantially impact the relative treatment effect in a sensitivity analysis of IPD from an earlier datacut of E1912.
Population 2: FCR-unsuitable patients Patients with no del17p mutation, with CIRS >6 and/or CrCl <70 mL/min	This population best reflects the cohort of the trial GLOW. The ITT cohort of GLOW, used in the economic model, includes some patients with TP53 mutation. Removal of patients with TP53 mutation from the dataset is possible, but comes at the cost of the following considerations: • Removal of TP53-mutated patients breaks the randomisation vs. O-Clb. In the recent appraisal TA689 (with more high-risk patients included than in GLOW), the NICE committee concluded that the percentage of these patients was low in the trial and any potential benefits from removing them would not be worth breaking randomisation. • High-risk patients (del17p/TP53 mutation) cannot be removed from the aggregate data for comparators (from CLL14 and ELEVATE-TN), given that IPD for these patients is not available. GLOW excluded patients with del17p, so leaving the patients with TP53 mutation in the GLOW ITT at least allows for adjustment for one of the high-risk characteristics.
Population 3: High-risk patients Patients with del17p/TP53 mutation	CAPTIVATE FD cohort included patients with del17p/TP53 mutation and provide insights in outcomes of high-risk patients when treated with I+V. There is a high unmet need for this poor prognostic population, and both physicians and patients have expressed they would welcome a new treatment option.

CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; del17p = 17p deletion; ECOG = European Cooperative Oncology Group; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; ITT = intent-to-treat; I+V = ibrutinib + venetoclax; NICE = National Institute for Health and Care Excellence; O-Clb = obinutuzumab + chlorambucil; PS = performance status; TP53 = tumour protein 53

B.3.2.2 Intervention technology and comparators

The intervention technology in the model is combination therapy with I+V. As stated in B.1.1 Decision problem, the relevant comparators in the model depend on the patient population:

- FCR-suitable patients: FCR
- FCR-unsuitable patients: O-Clb, VenO and acalabrutinib monotherapy
- High-risk patients: VenO, acalabrutinib monotherapy, and ibrutinib monotherapy

There is a difference in the number of cycles of Clb used in the control arm of the CLL14 trial (12 cycles) and the number of cycles in the control arm of the GLOW or ELEVATE-TN trial (6 cycles). 6 cycles of Clb are used in UK clinical practice.(60) Based on VenO's appraisal (1), the overall dose is likely to have a larger impact on efficacy than the number of cycles – this was further confirmed during an advisory board of clinical (n=5) and health economic experts (n=3) conducted in March 2022.(4) The overall dose of Clb used across trials is comparable for a typical patient.

The treatments and dosing for the FCR-suitable population, FCR-unsuitable population, and high-risk population are summarised in Table 22, Table 23, and Table 24, respectively.

Table 22 Treatments and dosing for FCR-suitable population

Regimen	Agent	Route	Duration	Dosing	Source
I+V	Ibrutinib	Oral	FD: for a total of 15 cycles	420 mg daily for 15 cycles	GLOW trial; November 2021 CSR(70)
	Venetoclax	Oral	FD: for a total of 12 cycles	5-week ramp up (20-400 mg daily) starting Day 1 of Cycle 4, then 400 mg daily	
FCR	Fludarabine	IV	FD: for a total of 6 cycles	25 mg/m^2 on days 1-3 for 6 cycles	MabThera 100 mg Concentrate for Solution for Infusion(55)
	Cyclophosphamide	IV	FD: for a total of 6 cycles	250 mg/m^2 on days 1-3 for 6 cycles	
	Rituximab	IV	FD: for a total of 6 cycles	375 mg/m^2 for the first cycle, then 500 mg/m^2 for the next 5 cycles	

CSR = clinical study report; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; mg = milligram; IV = intravenous I+V = Ibrutinib + venetoclax
All cycles comprise 28 days

Table 23 Treatments and dosing for FCR-unsuitable population

Regimen	Agent	Route	Duration	Dosing	Source
I+V	Ibrutinib	Oral	Same as above (Table 22)		GLOW trial; November 2021 CSR(70)
	Venetoclax	Oral			
O-Clb	Obinutuzumab	IV	FD: for a total of 6 cycles	1,000 mg administered over Days 1 (100mg) and 2 (900mg), 1000 mg on Day 8 and Day 15 of treatment Cycle 1, followed by 1,000 mg on Day 1 of treatment Cycles 2–6	Gazyvaro 1,000 mg concentrate for solution for infusion(59)
	Chlorambucil	Oral	FD: for a total of 6 cycles	0.5 mg/kg body weight twice (Days 1 and 15) of every cycle	
VenO	Venetoclax	Oral	FD: for a total of 12 cycles	5-week ramp up (20-400 mg daily) starting Day 22 of Cycle 1, then 400 mg daily	Venclyxto 100 mg film-coated tablets(8)
	Obinutuzumab	IV	FD: for a total of 6 cycles	1000 mg administered over Days 1 (100mg) and 2 (900mg), 1000 mg on	

Regimen	Agent	Route	Duration	Dosing	Source
				Day 8 and Day 15 of treatment Cycle 1, followed by 1000 mg on Day 1 of treatment Cycles 2–6	
Acalabrutinib monotherapy	Acalabrutinib	Oral	Treat to progression	100 mg twice daily till progression or unacceptable toxicity	Calquence 100 mg hard capsules(61)

C = cycle; CSR = clinical study report; D = day; FD = fixed duration; mg = milligram; IV = intravenous; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab. All cycles comprise 28 days

Table 24 Treatments and dosing for high-risk population

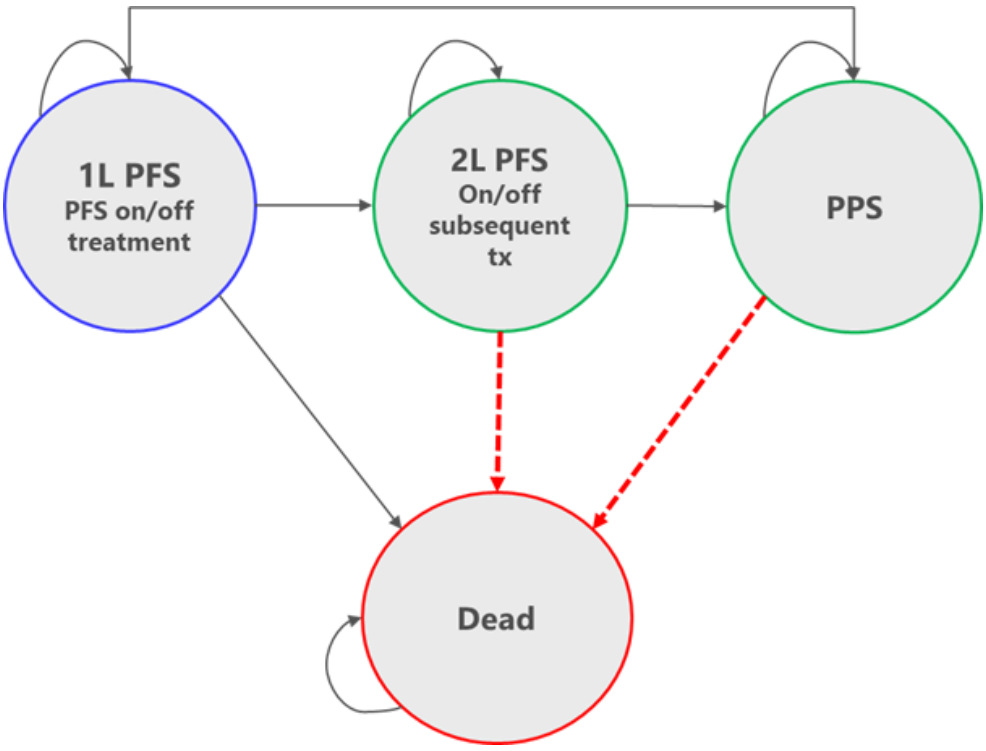
Regimen	Agent	Route	Duration	Dosing	Source
I+V	Ibrutinib Venetoclax	Same as above (Table 22 and Table 23)			GLOW trial; November 2021 CSR(70)
VenO	Venetoclax Obinutuzumab	Same as above (Table 23)			Venclyxto 100 mg film-coated tablets(8)
Acalabrutinib monotherapy	Acalabrutinib	Same as above (Table 23)			Calquence 100 mg hard capsules(61)
Ibrutinib monotherapy	Ibrutinib	Oral	Treat to progression or unacceptable toxicity	420 mg once daily	Imbruvica 420 mg film-coated tablets(13)

C = cycle; CSR = clinical study report; D = day; mg = milligram; IV = intravenous I+V = ibrutinib + venetoclax; VenO = venetoclax + obinutuzumab. All cycles comprise 28 days.

B.3.2.3 Model structure

The cost-effectiveness model utilised a semi-Markov structure with four mutually exclusive health states: progression free in first-line treatment (PF 1L), progression free in second-line treatment (PF 2L), disease progression (PPS) and death (Figure 19). The model explicitly considered up to two lines of active treatment. Unlike a conventional Markov, the semi-Markov model captures and follows each cohort of patients entering the PF 2L state in each cycle using tunnel states.

Figure 19 Model structure



1L = first-line; 2L = second-line; PFS = progression-free survival; PPS = post-progression survival; tx = treatment

State occupancy was modelled at four-week intervals (28 days) over the course of the modelled time horizon (40 years for FCR-suitable patients and 30 years for FCR-unsuitable and high-risk patients). Costs were assigned to each health state, and utilities were applied according to the patients' disease progression status. As the model progressed cycle by cycle for the duration of the time horizon, cost and utility data were summed per treatment arm, allowing for calculation of costs and comparative

effectiveness at model completion. Total costs and QALYs per treatment were estimated by combining the proportion of patients in each health state over time.

Health states

The health states included within the model were:

1) PF 1L: All patients in the model began on active treatment in the PF 1L state and could either remain in this state, progress, or die during each cycle. Depending on the nature of first-line treatment (FD or treat to progression), patients could be off active treatment for a period of time in PF 1L.
    i. Once patients progressed from 1L, they either began the next line of active therapy (PF 2L state) or received best-supportive care (BSC; PPS state).
2) PF 2L: Patients in the PF 2L state remained in this state until disease progression or death. Similar to PF 1L, patients could remain on active treatment for the time in PF 2L if they received a treat to progression regimen, such as a Bruton's tyrosine kinase inhibitor (BTKi), or up to a fixed period of time (if they received a FD regimen such as venetoclax + rituximab [VenR]).
    i. Following progression after first-line treatment, the base case assumes a delay of 14 cycles (based on TA689 ERG preferred scenario(9)) before initiating second-line treatment, to reflect what often happens in clinical practice.
3) PPS: Captured patients who have progressed during second-line treatment or those who progressed during first-line treatment that do not receive an active second-line treatment; patients in the PPS state received BSC but no active treatment. Patients in the PPS state remained on BSC until death.
4) Death: Captured patients who died in any other health state. The death state is an absorbing state, meaning patients transitioning to this health state are assumed to occupy it indefinitely.

Transitions

The transitions possible within the model are described in further detail below:

1) Transition from PF 1L to either PF 2L or PPS: Modelled using PFS curves and assumptions around pre-progression mortality.
    i. Although the individual PLD for the time to progression endpoint was available for within-trial comparators which could be used to model the transition from PF 1L to PF 2L or PPS, PFS was more broadly available to compare with external comparators.
    ii. Since PFS is a composite endpoint which includes both progression and death events, the pre-progression mortality is subtracted from the PFS hazard rate to derive the transition probabilities for those who progress on their first-line treatment and remain alive to receive a subsequent treatment or post 2L progression time.
    iii. The model has the functionality to specify the proportion of patients who are eligible to receive a second-line treatment upon progression. A subset of eligible patients transitions from PF 1L to PF 2L, while the remaining patients transition from PF 1L to the PPS state.
2) Transition from PF 1L to death: Informed by mortality in PFS (pre-progression mortality).
    i. The trial-derived mortality estimates in the model are constrained by general population mortality (GPM) to ensure that the survival never exceeds that of the general population.
3) Transition from PF 2L to PPS: Derived from external PFS data representative of R/R CLL patients who are progression free.
    i. As in PF 1L, the composite PFS endpoint is broken down into progression and death events by subtracting the mortality in PF 2L from the PFS hazard rate. Patients who experience progression events in PF 2L transition to PPS where they receive BSC.
4) Transition PF 2L to death: Derived from external data representative of R/R CLL patients who are progression free.

i. Using annual mortality data from the external source, a constant probability of death per cycle was computed and applied throughout the model horizon. Similar to PF 1L, the transition probabilities are capped by GPM.

5) PPS to death: The transition probabilities for PPS to death were handled similarly to that of PF 2L to death.

The clinical parameters and variables used to inform the analyses are described in detail in the next section.

B.3.3 Clinical parameters and variables

B.3.3.1 Input sources for clinical efficacy

As a result of using a semi-Markov model, individual survival analyses were required for each possible transition. ITCs were required to inform transitions between health states for external comparators. The data sources summarised in Table 25 informed the clinical parameters for the three populations.

The following sections describe the transition probabilities and additional details for the individual populations of interest: B.3.3.2 FCR-suitable , B.3.3.3 FCR-unsuitable population and B.3.3.4 High-risk population.

Table 25 Summary of data sources informing the clinical parameters

Population	Clinical trial	Median Follow-up	IPD available	Use of trial in analysis	Trial features/limitations	Justification
FCR-suitable population	CAPTIVATE	38.7 months (68)	Yes	I+V PFS 1L used to derive HR vs. FCR	FCR-suitable population Phase II single arm trial assessing the FD cohort˜; FD cohort with no del17p is used for modelling purposes	• The only data available for I+V use in FCR-suitable population
	E1912	36.6 months (89)	Yes	Death during PFS	I+R vs. FCR Excluded del17p	• Phase 3 RCT • Long-term follow-up available (median 70 months) • IPD data available for comparative efficacy • Relatively newer trial with long-term follow-up better capturing current CLL management†
		48 months (78)	Yes	A HR applied to FCR PFS curve informed I+V PFS curve		
		70 months (83)	No	FCR PFS 1L Validation of OS extrapolation	Long-term follow-up for FCR and BTKi	
	CLL8	71 months (90)	No	Validation of PFS extrapolation	FCR vs. FC Included higher risk patients who are no longer eligible to receive FCR (CIRS >6, CrCl <70mL/min and with del17p) Older trial that may not reflect current OS per clinical advisory board (4)	• Phase 3 RCT • Provides long term follow-up (median 71 years) for a slightly more severe population than CAPTIVATE

Population	Clinical trial	Median Follow-up	IPD available	Use of trial in analysis	Trial features/limitations	Justification
	CLL10	58.2 months (91)	No	Validation of PFS extrapolation	FCR vs. BR Excluded del17p patients, included some TP53 patients	• Phase 3 RCT • Provides long term follow-up for a similar population as CAPTIVATE FD but from a less current trial.
FCR-unsuitable population	GLOW	34.1 months (70)	Yes	I+V and O-Clb PFS 1L extrapolation; O-Clb mortality in PFS 1L for all comparators	I+V vs. O-Clb FCR-unsuitable population Excluded del17p Included age ≥65 years, **or** 18 to 64 years of age with CIRS score >6 and/or or CrCl <70 mL/min	• Phase 3 RCT • Provides head-to-head data for I+V vs. O-Clb • PLD available • The only data available for I+V use in FCR-unsuitable population
	CLL14	28.1 months (80)	No	Comparative efficacy vs. I+V (has O-Clb as common comparator which enables an anchored MAIC)	VenO vs. O-Clb FCR-unsuitable population; Included some del17p patients Included age ≥18 years and either total CIRS score >6 and/or CrCl <70 mL/min	• Phase 3 RCT • Use of similar follow-up to I+V for comparative efficacy • Use the longest available data to validate extrapolations
		52.4 months (53)	No	PFS curve for validation Used to inform I+V PFS shape parameter in scenario analysis[†]		
	ELEVATE-TN	28.3 months (92)	No	Comparative efficacy vs. I+V (has O-Clb as common comparator which	Acalabrutinib vs. O-Clb FCR-unsuitable population;	• Phase 3 RCT • Use of similar follow-up to I+V for comparative efficacy

Population	Clinical trial	Median Follow-up	IPD available	Use of trial in analysis	Trial features/limitations	Justification
				enables an anchored MAIC)	Included some del17p patients Included age ≥65 years, or 18 to 64 years of age with a CIRS score >6, CrCl <70 mL/min or diagnosis of CD20+ CLL	• Use the longest available data to validate extrapolations
		46.9 months (93)	No	PFS curve for validation		
	RESONATE-2	88.5 months (6)	No	Validation of PFS and OS extrapolation	Ibrutinib vs. ofatumumab FCR-unsuitable population Excluded del17p Long-term follow-up for a BTKi and targeted agents in CLL in general.	• Phase 3 RCT • Use the longest available data to validate extrapolations
FCR-suitable, FCR-unsuitable, and high-risk populations	RESONATE (1-2 prior lines subgroup)	65 months (94)	Yes	PFS 2L, death during PFS 2L and post progression mortality for all comparators	Ibrutinib vs. ofatumumab R/R CLL population The median age of patients in RESONATE (68 years) is younger than the starting age of the FCR-unsuitable population 71 years derived from the GLOW trial)	• Phase 3 RCT • Immature OS data in both GLOW and CAPTIVATE trials necessitates the use of external data • Ibrutinib arm from RESONATE (1-2 prior line subgroup) provides a proxy for the PFS of patients progressing after first-line therapy. This was preferred over other trials with long-term follow-up (70m

Population	Clinical trial	Median Follow-up	IPD available	Use of trial in analysis	Trial features/limitations	Justification
						E1912) due to the access of IPD and as it explicitly captures the prognosis of R/R CLL patients receiving a targeted agent (BTKi) • R/R CLL patients are similar across populations • Post-progression survival from RESONATE (1-2 prior line) was used in the NICE evaluation of acalabrutinib in first-line CLL of an FCR-unsuitable population.(2)

1L = first line; 2L = second line; BR = bendamustine + rituximab; BTK = Bruton's tyrosine kinase; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CrCl = creatinine clearance; del17p =17p deletion; FC = fludarabine, cyclophosphamide; FCR = fludarabine, cyclophosphamide, rituximab; FD = fixed duration; HR = hazard ratio; I+R = ibrutinib + rituximab; I+V = ibrutinib + venetoclax; IPD = individual patient data; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; O-Clb = obinutuzumab + chlorambucil; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; R/R = relapsed/refractory

[†] CLL8 study started in 2003 and enrolment ended in 2006; CLL10 trial primary completion in 2011; E1912 stated in February 2014; [†] GLOW I+V PFS' shape parameter was informed by the shape parameter of CLL14's VenO extrapolations (52.4m) in a Bayesian framework.

[~] CAPTIVATE is an international, multi-centre, phase II, 2-cohort clinical trial, including the FD cohort (the focus of this submission for CAPTIVATE) and the MRD cohort where patients are assessed during a pre-randomization phase (ibrutinib lead-in followed by combination I+V treatment), an MRD-guided randomisation phase, and a post-PD follow-up phase

B.3.3.1 Approaches to extrapolation

The clinical trials used to inform clinical outcomes only provided survival data up to a limited follow-up time. To apply a lifetime perspective in the cost-effectiveness analysis, extrapolations of clinical outcomes beyond the trial follow-up period were necessary. Extrapolations of PFS were done in line with methods in Decision Support Unit (DSU) Technical Support Document (TSD) 14 and TSD 21,(95, 96) using parametric survival analyses, spline analyses and Bayesian parametric survival analyses. Goodness of fit was assessed by Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and comparing observed and predicted data. Due to immaturity of the available PFS data, selection of the approach and distribution for extrapolation was mainly driven by clinical plausibility of long-term predictions.

Appendix O.1 provides details of the various methodologies explored to extrapolate clinical efficacy data beyond the trial follow-up period. The choice of the reference curves and the methodology of indirect comparisons are described in B.2.9

Indirect and mixed treatment comparisons.

B.3.3.2 FCR-suitable population

There are five relevant clinical transitions in the FCR-suitable population (summarised in Table 26):

- the transition from PF 1L to PF 2L or PPS
- the transition from PF 2L to PPS
- the transitions from the three alive states (PF 1L, PF 2L, PPS) to the death state

Table 26 Summary of transition probabilities between health states for the FCR-suitable population

Transitions	Measure	FCR-suitable	
		I+V	FCR
PF 1L to PF 2L or PPS	PFS 1L	HR applied to E1912 FCR curve HR derived from propensity score analysis using FD cohort from CAPTIVATE trial (68) and E1912 trial (89)	Reference Curve: Parametric survival model for E1912 data (83) Weibull fitting
PF 1L to Death	Death during PFS 1L	Annual mortality based on the FCR arm of the E1912 trial (89)	
PF 2L to PPS	PFS 2L	Parametric survival model based on ibrutinib arm of RESONATE (1-2 prior lines subgroup) for all treatments.(94) Exponential fitting	
PF 2L to Death	Death during PFS 2L	Mortality rate during 2L PFS based on ibrutinib arm of RESONATE (1-2 prior lines subgroup) for all treatments (94)	
PPS to Death	Post 2L progression	Mortality rate during post 2L progression based on ibrutinib arm of RESONATE (1-2 prior lines subgroup) (94)	

1L = first line; 2L = second line; FCR = fludarabine, cyclophosphamide, rituximab; FD = fixed duration; I+V = ibrutinib + venetoclax; PF = progression free; PFS = progression-free survival; PPS = post-progression survival

PF 1L to PF 2L or PPS

Base case: FCR PFS - E1912 trial, Weibull distribution; I+V – PFS HR applied to E1912 curve (Table 26)

PFS reference curve

As outlined in Table 25, several sources of data were explored for informing the model PFS reference curve and other clinical inputs:

- CAPTIVATE trial FD cohort
- FCR arm from E1912
- FCR arms from CLL8 and CLL10 trials

The use of INV-assessed PFS from the CAPTIVATE trial FD cohort (no del17p subgroup) was not used to inform I+V PFS long-term extrapolation due to immature data.

- In the extended follow up of 38.7m, [redacted] (Figure 7). At [redacted] months, the I+V PFS rate in the FD cohort (no del17p subgroup) was [redacted]
- From visual inspection of the observed data (Figure 7), it is clear that the PFS data from CAPTIVATE for the FD cohort excluding del17p patients is immature. [redacted] This pattern is different from the pattern observed in the GLOW trial (B.3.3.3 FCR-unsuitable population), in which PFS events occurred early and then the PFS plateaued.

CAPTIVATE FD was also a non-comparative (single-arm) cohort, thus, external data were required to provide the comparative efficacy against FCR, which was the most relevant comparator. External data sources that were available for FCR and details about these are summarised in Table 25.

Given the highly immature PFS data from CAPTIVATE, alternative sources of data were assessed to inform the PFS reference curve in the model. Instead, the E1912 trial was chosen to inform FCR PFS, due to IPD being available (facilitates ITC vs. I+V) and provides long-term follow up for extrapolation. The E1912 trial provided the INV-assessed PFS data for the previously untreated FCR-suitable population.

- This trial was preferred to other sources of FCR data, since Janssen had access to IPD from the 36.6m and 48m median follow-up and were able match the populations of CAPTIVATE and E1912 trials for ITC analyses using the IPTW approach (B.2.9 Indirect and mixed treatment comparisons) and also estimate transition for death during PFS.

- In addition, long-term follow up data (70m median follow up) from E1912 were published. These data were digitised and converted to virtual patient-level data (VPLD) using Guyot method and used for long-term extrapolation of FCR arm in the model.

CLL8 (90) and CLL10(91), which also evaluate the clinical efficacy of FCR in an FCR-suitable population, were not used to inform FCR PFS in the model because IPD are not available and the CLL8 trial differed in several ways from CAPTIVATE (Table 25 and Appendix D.1.8.2). From comparison of the PFS KM data, the CLL10 and E1912 appear very similar and have equivalent follow-up (Figure 20), but as noted, E1912 was preferred due to the availability of IPD for earlier data cuts(89) which enabled the propensity score based analyses between the I+V arm from the CAPTIVATE trial vs. the FCR arm from E1912 (ITC described in B.2.9 Indirect and mixed treatment comparisons).

Figure 20 Naïve comparison of FCR PFS KM from E1912 (70m median), CLL8 (71m), and CLL10 (58.2m)

CLL = chronic lymphocytic leukaemia; FCR = fludarabine + cyclophosphamide + rituximab; KM = Kaplan-Meier; PFS = progression-free survival

PFS parametric fits

FCR

Survival data from the E1912 trial (Figure 20) was used to inform PFS for FCR (70 months [5.8 years] median follow-up).(83) The PFS data were mature with a 5 year PFS rate of 51% reported for the FCR arm (i.e., nearly a 5 year median). The published data for PFS were digitised and then converted to VPLD using the methodology described in Guyot et al.(97) The accuracy of the VPLD data was checked by comparing observed vs. estimated using VPLD medians and number at risk over time. Parametric survival analyses were then conducted using VPLD.

A summary of the goodness-of-fit statistics for the INV-assessed PFS for FCR in E1912 (70m data cut) is presented in Table 27.

Table 27 Goodness-of-fit statistics (AIC/BIC) for the parametric models fitted to INV PFS KM data for FCR in E1912

Distribution	AIC	BIC	Median PFS without capping (years)
Exponential	449.61	452.75	[redacted]
Weibull	447.88	454.14	[redacted]
Log-logistic	449.31	455.57	[redacted]
Log-normal	454.26	460.52	[redacted]
Gamma	449.89	459.24	[redacted]
Gompertz	448.47	454.73	[redacted]

AIC = Akaike information criteria; BIC = Bayesian information criteria; PFS = progression-free survival

Figure 21 shows the parametric extrapolations with and without capping by GPM hazard overlaying the PFS INV KM data for FCR from E1912.

Figure 21 Parametric models overlaying the observed INV PFS KM data for FCR from E1912

FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; KM = Kaplan-Meier; PFS = progression-free survival

Table 28 shows the landmark PFS estimates for the standard parametric functions fitted to the observed I+V INV PFS data from E1912 which helped assess clinical plausibility of extrapolations.

Table 28 Landmark PFS estimates for the FCR INV PFS data from E1912 when capped by GPM

Distribution	1-year	2-year	5-year	10-year	15-year	20-year	30-year
Exponential							
Weibull							
Log-logistic							
Log-normal							
Gamma							
Gompertz							

FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; INV = investigator; PFS = progression-free survival

Based on visual inspection of standard parametric functions fitted to the E1912 PFS curves (Figure 21) and the AIC/BIC values, all distributions provide similar fits to the observed data. Weibull and exponential are the best fitting distributions in terms of the AIC/BIC values. However, long-term extrapolations differ across the fitted distributions.

The Weibull projection was chosen as the base case extrapolation based on the clinical plausibility of long-term extrapolations (Weibull yield a 5-year PFS estimate of [redacted] and E1912 estimates [redacted] PF patients at ~5 years).(4)

I+V

The I+V PFS was estimated by applying a HR derived from the propensity score matching (described in B.2.9 Indirect and mixed treatment comparisons and Appendix D.1.8.2) to the FCR reference curve. Table 29 shows the PFS HR of I+V vs. FCR using the weighting for the E1912 trial (ATC approach) as well as weighting based on the I+V PFS from CAPTIVATE FD (ATT approach), and an average treatment effect in the combined/overall populations of the two trials (ATO approach). The ATC analysis in which the CAPTIVATE FD cohort is matched to E1912 FCR group for all treated patients was considered as the base case, given that the E1912 FCR PFS is used as the reference curve. The analysis excluding patients with missing covariate values was selected as this analysis showed better balance between covariates for the populations (see Appendix D.1.8.2). The ATO, which reflects an overlapped population, and ATT, which reflects a population matched to the CAPTIVATE FD cohort were explored in scenario analyses. The HRs in these analyses were relatively consistent across analyses (see B.2.9 Indirect and mixed treatment comparisons) and are also consistent with the HR seen for I+R vs. FCR in the E1912 trial, where the PFS HR from over 70 months of follow-up was 0.37 ($p<0.001$).(83)

Table 29 PFS HR of I+V vs. FCR for the ATC, ATO and ATT analyses based on the adjusted populations in the CAPTIVATE FD cohort (no del17p) and E1912

Analysis	All treated patients without del17p excluding any missing covariate values	Mean HR (95% CI)
ATC (Base case)	Excluded	[redacted]
ATO (Scenario)	Excluded	[redacted]
ATT (Scenario)	Excluded	[redacted]

ATC = average treatment effect in the control population; ATO = average treatment effect in the combined/overall population; ATT = average treatment effect in the treated population; CI = confidence interval; del17p = 17p deletion; HR = hazard ratio

Figure 22 shows the parametric extrapolations of the I+V PFS from the CAPTIVATE FD cohort (no del17p) based on the derived HR vs. the FCR arm from E1912. It is clear from visual inspection that standard parametric functions cannot capture the steep drop observed in the PFS curve (the second drop in the PFS curve is artificial due to the low number of patients at risk). This shape is a result of short recruitment time in CAPTIVATE FD which leaves very few patients at risk at the last months of follow-up time due to censoring which amplifies the impact of any events observed during this period on KM curve. The shape is expected to change with further follow-up.

Figure 22 I+V PFS capped by GPM derived from the HR vs. FCR reference curve (ATC analyses)

del17p = 17p deletion; FD = fixed duration; GPM = general population mortality; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; PFS = progression-free survival
I+V applied to the Weibull distribution from FCR PFS extrapolation

Table 30 shows the landmark PFS estimates for the I+V PFS arm from CAPTIVATE derived from the FCR reference curve which helped analyse the clinical plausibility of the extrapolations.

Table 30 Landmark PFS estimates for I+V PFS from CAPTIVATE derived from the FCR reference curve

Distribution	1-year	2-year	5-year	10-year	15-year	20-year	30-year
Weibull for FCR reference curve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			E1912 I+R arm: [redacted]				

FCR = fludarabine + cyclophosphamide + rituximab; I+R = ibrutinib + rituximab

Since an independent fit to the I+V arm was ruled out due to data immaturity, the current base case approach of applying a HR derived from the ATC analysis vs. the exponential FCR curve is reasonable. The estimated PFS at 5 years is [redacted] for I+V vs. [redacted] for the I+R arm of the ECO1912 trial. The resulting estimate for I+V FD is slightly lower when compared with long-term data from the I+R arm of the E1912 trial.

Scenario analyses based on the FCR extrapolations (exponential, gompertz and gamma) and the HR of I+V PFS vs. FCR (ATT, ATO methods in all treated population) were conducted to understand the impact on the results.

PF 1L to Death

Base case: Pre-progression mortality derived from FCR arm of E1912 and applied to FCR and I+V arms (Table 26)

To estimate the deaths from the composite endpoint of PFS, an annualised mortality rate was applied to PFS. Pre-progression deaths observed in the CAPTIVATE FD cohort (no del17p) and E1912 FCR arm (36.6m data cut) from PLD were used to assess mortality rate during PFS for the model. The annualised mortality rate derived from the FCR arm of the E1912 trial CAPTIVATE FD cohort (no del17p) was converted to a transition probability from PF to death and was assumed to be a constant probability per cycle throughout the model horizon.

To ensure logical consistency, the transition probabilities were capped by age and gender adjusted GPM rate (98) which was derived from the National Life Tables 2018-

2020 for England (qx: death probability between age x and x+1) published by the Office for National Statistic. This ensured that the probability of dying in pre-progression is never lower than the probability of dying due to GPM.

Table 31 shows the annual mortality rate in PFS for the I+V and FCR arms based on total follow-up days and the number of death events occurring during PFS in CAPTIVATE FD cohort (no del17p) and E1912 respectively.

Table 31 Annual mortality rate in PFS derived from CAPTIVATE FD cohort (no del17p) and E1912

Treatment	Total PFS Patient Years	Total PFS Death	Annual mortality rate in PFS
I+V	[redacted]	[redacted]	[redacted]
FCR (used for both arms in model)			

FCR = fludarabine + cyclophosphamide + rituximab; I+V = ibrutinib + venetoclax; PFS = progression-free survival

The hazard of pre-progression mortality for FCR derived from E1912 (36.6m data cut) coincides with that of the general population at approximately 5 years as shown in the hazard plots (Appendix O.3) where a change in the curve from a straight line coincides with the stepwise increase in mortality risk. The pre-progression mortality hazard for I+V converged with that of the GPM from the first cycle, meaning the pre-progression mortality of I+V patients with previously untreated CLL is the same as that of the UK general population. This may be unrealistic in the longer term, so the model assumes a pre-progression mortality derived from E1912 (36.6m data cut) capped by GPM for both the I+V and the FCR arms. The pre-progression mortality of the I+V and FCR arms compared with GPM is shown in Appendix O.3.

PF 2L to PPS

Base case: All subsequent treatments - PFS from ibrutinib arm of RESONATE (1-2 prior lines subgroup). Exponential distribution (Table 26)

Reference curve

Patients who experience disease progression while receiving first-line treatment may receive a subsequent active treatment with ibrutinib, acalabrutinib or VenR. For ibrutinib

and acalabrutinib, the duration of treatment aligns with PFS since these are given as treat to progression. In the case of VenR, the duration of treatment is only up to 24 cycles per the indication.

IPD for patients who received ibrutinib in 2-3 line (i.e., 1-2 prior lines) in the RESONATE trial with a median follow-up of 65 months (final analysis; shown in Figure 23 and Appendix P.2), was analysed to inform the reference curve for second line PFS. This subgroup did not include heavily pre-treated patients that would bias the efficacy outcome and was therefore assumed to represent the prognosis of the FCR-suitable CLL patients upon progression in the current treatment landscape. RESONATE trial was preferred over E1912 to estimate post-progression survival for several reasons:

1) data from the ibrutinib arm of RESONATE reflects the disease prognosis of patients receiving a targeted agent (BTKi) in the R/R CLL setting(2),
2) long-term data are available, and
3) access to IPD was not available to estimate post-progression transitions.

To derive the reference curve for second line treatment PFS during and beyond the observed period of data in the RESONATE trial, parametric survival analyses (see the approach described in Appendix O.1) of the subgroup of patients with 1-2 prior lines of treatment in the ibrutinib arm was conducted.

A summary of the goodness-of-fit statistics for the 2L PFS endpoint, estimated from the ibrutinib arm of the RESONATE trial final (65m) data cut (1-2 prior line subgroup), is presented in Table 32.

Table 32 Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to INV PFS data for ibrutinib (1-2 prior line subgroup) from the RESONATE trial final (65m) data cut

Distribution	AIC	BIC	Median PFS without capping for GPM (years)
Exponential	497.81	500.29	[redacted]
Weibull	499.65	504.56	[redacted]
Log-logistic	501.03	505.94	[redacted]
Log-normal	504.91	509.82	[redacted]
Gamma	501.28	508.58	[redacted]

Distribution	AIC	BIC	Median PFS without capping for GPM (years)
Gompertz	499.28	504.19	[redacted]

AIC = Akaike information criteria; BIC = Bayesian information criteria; GPM = general population mortality; PFS = progression-free survival

Figure 23 shows the parametric extrapolations overlaying the PFS INV KM data for ibrutinib (1-2 prior line subgroup) from the RESONATE trial final (65m) data cut.

Figure 23 PFS extrapolations of ibrutinib (1-2 prior lines) from RESONATE trial final (65m) data cut

PFS = progression-free survival

Table 33 shows the landmark PFS estimates for ibrutinib (1-2 prior line subgroup no del17p) from the RESONATE trial final (65m) data cut.

Table 33 Landmark PFS estimates for the I+V INV PFS data for ibrutinib (1-2 prior line subgroup) from the RESONATE trial final (65m) data cut

Distribution	1-year	2-year	5-year	10-year	15-year	20-year	30-year
Exponential	[redacted]						
Weibull							
Log-logistic							
Log-normal							
Gamma							
Gompertz							

I+V = ibrutinib + venetoclax; INV = investigator; PFS = progression-free survival

Based on the goodness of fit statistics, all distributions provided similar and good fit to the observed data. The estimated median PFS is approximately 6 years for all standard parametric functions. The exponential distribution was selected due to its constant hazard nature as the model cannot track the survival of patients stratified by the cycle of progression. It so happens that the exponential distribution provides the best fit to the observed data (i.e., AIC and BIC) and long term extrapolations are in the middle between the most optimistic scenario (i.e., log-normal) and pessimistic scenario (i.e., generalised gamma). Both the log-logistic and log-normal models were ruled out as the relatively flatter tail upon reaching median PFS seemed unrealistic.

Comparative efficacy

In the base case, the PFS associated with all second line treatments is assumed to be the same and reflect the reference curve estimated from RESONATE data (subgroup with 1-2 prior lines of treatment in the ibrutinib arm). The clinical equivalence of ibrutinib continuous use and acalabrutinib in the R/R CLL setting was accepted in the TA689 given outcomes of an ITC.(2) Assuming the same clinical equivalence across subsequent treatments was an assumption used and accepted in prior NICE appraisals (TA663 and TA689).

PF 2L to Death

Base case: All treatments use annual mortality rate during 2L PFS based on ibrutinib arm of RESONATE (1-2 prior lines subgroup) (Table 26)

Reference curve

Since the data from the CAPTIVATE FD cohort were immature to provide information on mortality during second line PFS, external data from the ibrutinib arm of the RESONATE trial final (65m) data cut (1-2 prior line subgroup) was used to calculate an annual mortality rate. The annual mortality rate was converted into a constant probability of death per cycle while patients are progression free during second line treatment. The probability of death during second line treatment is capped by the corresponding age and gender adjusted GPM to prevent logical inconsistencies.

Table 34 shows the annual mortality rate for the ibrutinib arm (1-2 prior line subgroup) based on total follow-up days and number of death events occurring during PFS in RESONATE.

Table 34 Annual mortality rate in PF 2L derived from RESONATE Ibrutinib arm (1-2 prior line subgroup)

Treatment	Total PFS Patient Years	Total PFS Death	Annual mortality rate in PFS
Ibrutinib 1-2 prior line	[redacted]	[redacted]	[redacted]

PFS = progression-free survival

The annual mortality rate is converted to a constant probability of death per cycle which is capped by the corresponding age adjusted GPM. While the risk of dying in subsequent line PFS remains constant throughout the model horizon, the risk of dying due to GPM increases with age.

Relative treatment effects

In the base case, the mortality risk associated with all second line treatments is assumed to be the same and reflect the RESONATE trial ibrutinib arm data (1-2 prior line subgroup), given there is no current evidence to show otherwise.

PPS to Death

Base case: All treatments use annual mortality rate during 2L post-progression based on ibrutinib arm of RESONATE (1-2 prior lines subgroup) (Table 31)

Reference curve

PPS follows the same approach used for death in second-line PFS, with a constant annual mortality rate derived from the post-progression data from the RESONATE trial ibrutinib arm (1-2 prior line subgroup) and capped by the general population hazards.

Table 35 shows the annual mortality rate for the ibrutinib arm (1-2 prior line subgroup) based on total follow-up days and number of death events occurring during PPS in RESONATE

Table 35 Annual mortality rate in 2L PFS derived from RESONATE Ibrutinib arm (1-2 prior line subgroup)

Treatment	Total PPS Patient Years	Total PPS Death	Annual mortality rate in PPS
Ibrutinib 1-2 prior line subgroup	[redacted]	[redacted]	[redacted]

PPS = post-progression survival

Comparative efficacy

Based on clinician feedback, patients may continue to receive treatments beyond progression on second-line treatment in the current treatment landscape. However, there are no clinical data on the treatment efficacy beyond progression on second line treatment in an FCR-suitable population or otherwise. Given the data uncertainty, it is assumed that treatments will not have any effect on survival. Only the annual risk of death is modelled, and it is informed by the post-progression risk of death in the ibrutinib arm subgroup with 1-2 prior lines of treatment from RESONATE trial. A constant annualised risk of death of [redacted] is applied.

B.3.3.3 FCR-unsuitable population

There are five relevant clinical transitions in the FCR-unsuitable population (summarised in Table 36):

- the transition from PF 1L to PF 2L or PPS
- the transition from PF 2L to PPS
- the transitions from the three alive states (PF 1L, PF 2L, PPS) to the death state

Table 36 Summary of transition probabilities between health states for the FCR-unsuitable population

Transitions	Measure	Section	I+V	O-Clb	VenO/ Acalabrutinib
PF 1L to PF 2L or PPS	INV PFS	PF 1L to PF 2L or PPS	I+V KM data for the first 15 cycles to capture early mortality followed by parametric survival models applied to GLOW data;(70) Exponential fitting	Spline model (7 knots) from GLOW (70)	Anchored MAIC: I+V vs. comparator (refer to B.2.9 Indirect and mixed treatment comparisons): • I+V vs. VenO (GLOW and CLL14) • I+V vs. acalabrutinib (GLOW and ELEVATE-TN)
PF 1L to Death*	Death during PFS (to allocate patients to PF 2L or PPS [among those who progress while receiving 1L])	PF 1L to Death	KM data for first 15 cycles, and annual mortality based on O-Clb arm from GLOW (70) and constrained by GPM(98)	Annual mortality based on O-Clb arm from GLOW (70) and constrained by GPM(98)	Assumed to be the same as O-Clb, constrained by GPM
PF 2L to PPS	PFS	Post progression transitions (PF 2L to PPS, PF 2L to Death, PPS to Death)	Parametric survival model based on ibrutinib arm of RESONATE (1-2 prior lines) final (65m) follow-up for all treatments.(94) Exponential fitting		
PF 2L to Death*	Death during PFS		Mortality rate during 2L PFS based on ibrutinib arm of RESONATE (1-2 prior lines) final (65m) follow-up for all treatments.(94)		
PPS to Death*	Post second-line progression		Mortality rate during PPS based on ibrutinib arm of RESONATE (1-2 prior lines) final (65m) follow-up.(94)		

1L = first line; 2L = second line; CLL = chronic lymphocytic leukaemia; GPM = general population mortality; INV = investigator; MAIC = matching-adjusted indirect comparison; O-Clb = obinutuzumab + chlorambucil; PF = progression free; PFS = progression-free survival; PPS = post-progression survival; VenO = venetoclax + obinutuzumab; *Death is a self-absorbing health state. In other words, patients who transition to the death state do not leave the health state

PF 1L to PF 2L or PPS

Base case: I+V PFS – GLOW trial, KM for 15 cycles, followed by exponential distribution; O-Clb- GLOW trial, 7-knot spline curve (Table 36)

I+V PFS

The observed INV-assessed PFS data from the GLOW trial (70) at the extended follow up of median 34.1 months (KM shown in Figure 24) was used to estimate extrapolations of PFS 1L for I+V. In the I+V arm, the PFS shows the occurrence of early events followed by a plateau with few patients experiencing events.

INV-assessed PFS was selected rather than IRC-assessed PFS (GLOW primary endpoint), since only INV-assessed PFS was available for the external comparators (VenO and acalabrutinib).

Figure 24 Observed INV PFS data extended follow-up ( ) of the GLOW trial

I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil
Source: Janssen Research & Development LLC [Data on File], 2021(70)

Visual inspection of the KM data of I+V and O-Clb suggests that the PH and accelerated failure time (AFT) assumptions are violated. This was confirmed by further examination of cumulative hazard plots, Schoenfeld residual plots, the log-survival odds and normal quantiles plots. Appendix O.1.2 describes the test for PH and AFT assumptions in detail. Thus, parametric models fitted to each arm separately (independent) were considered for extrapolating PFS for I+V and O-Clb.

The extrapolations of I+V PFS from different models were assessed based on goodness-of-fit statistics, a comparison of observed vs. predicted survival and clinical plausibility.

Table 37 presents a summary of the goodness-of-fit statistics for the INV PFS endpoint of I+V from GLOW.

Table 37 Goodness-of-fit statistics (AIC/BIC) for the independent parametric models fitted to INV-assessed PFS data for I+V

Distribution	AIC	BIC	Median PFS without capping for GPM (years)
Exponential	225.24	227.86	[redacted]
Weibull	225.59	230.80	
Log-logistic	225.24	230.45	
Log-normal	223.86	229.07	
Gamma	223.76	231.51	
Gompertz	223.42	228.63	

AIC = Akaike information criteria; BIC = Bayesian information criteria; GPM = general population mortality; NE = not estimable; PFS = progression-free survival

Figure 25 shows the parametric extrapolations, with (dotted curves) and without capping (solid curves) by UK GPM, overlaying the INV-assessed PFS KM data for I+V.

Figure 25 Parametric models overlaying the observed INV-assessed PFS KM data for I+V

GPM = general population mortality; I+V = ibrutinib + venetoclax; INV = investigator; KM = Kaplan-Meier; PFS = progression-free survival

Table 38 shows the landmark estimates for the standard parametric functions fitted to the observed I+V INV PFS data from GLOW that were used to determine the clinical plausibility of extrapolations. These were validated by clinical expert opinion in May 2022.(5)

Table 38 Landmark estimates for the I+V INV PFS data from GLOW when capped by the UK GPM hazard

Distribution	6 month	1-year	2-year	5-year	10-year	15-year	20-year	30-year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
External data TA689	TA689 suggested that a PFS landmark rate of 70% at 5 years with BTKi was reasonable (2)							

Distribution	6 month	1-year	2-year	5-year	10-year	15-year	20-year	30-year
External data RESONATE-2	In RESONATE-2, PFS was 59% for ibrutinib at 7 years (6)							

BTKi = Bruton's tyrosine kinase inhibitor; PFS = progression-free survival; TA = technology appraisal

Based on fit statistics, all models provided similar fit for I+V INV PFS (Table 38) over the observed follow up; however, there was a large degree of variability in the predicted PFS over the model horizon (Figure 25). The generalised gamma, Gompertz and Weibull extrapolations predict the observed KM data well, especially within the first 3 months, but provide unrealistic long-term projections: predicting [redacted] progression free at 30 years, respectively. This was deemed implausible by the advisory board of clinical and health economic experts conducted in March 2022(4) because the curves reflect a highly optimistic prognosis for FCR-unsuitable CLL patients. In addition, the gamma and gompertz extrapolations never reach median PFS when not capped by GPM (which is clinically implausible) and converge to GPM within 5 years. Weibull, log-logistic and log-normal extrapolations converge with the GPM within 10 years. Although this is more reasonable than the gamma and gompertz extrapolations, the clinical plausibility of an FCR-unsuitable CLL patient becoming equivalent to a patient without the disease at any timepoint is uncertain.

The exponential extrapolation was selected in the base case analysis as this was the most conservative extrapolation in the long term and better aligned with external trial data and clinical opinion (per the advisory board of clinical and health economic experts conducted in March 2022).(4)

The RESONATE-2 trial (6) (which follows an FCR-unsuitable cohort with no del17p receiving ibrutinib monotherapy) demonstrated a PFS rate of 59% at 7 years. This external data acts as a secondary validation (Appendix P.1) for the exponential extrapolation of the I+V arm from GLOW, whose PFS at 7 years was [redacted]

Since the exponential distribution did not capture the early PFS events that occurred in the I+V arm in GLOW, PFS KM data from the GLOW trial was used for the first 15 cycles followed by an exponential distribution capped by GPM (shown in Figure 26).

Figure 26 PFS extrapolation of I+V capped by GPM (observed KM data + exponential model)

GPM = general population mortality; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; PFS = progression-free survival
Both the exponential and KM + exponential curves have been capped by GPM; The solid curves represent the projections uncapped by GPM and the dotted curves represent the projections capped by the GPM. Both the exponential and the KM + exponential extrapolation converges with the GPM at approximately 15 years.

Flexible survival models (Appendix O.1.3) were fitted but not used for I+V PFS since PFS data was immature which led to convergence problems with some models and a high risk of overfitting for others. Furthermore, for the models that converged, the low number of events at the tail of the KM curve led to clinically implausible long-term extrapolations requiring PFS to be capped by GPM after only a few years.

The shape parameter from VenO from the CLL14 trial was used to inform the shape of I+V in a Bayesian parametric survival analysis framework as a scenario analysis. Based on the I+V extrapolations (which used the VenO shape parameter as an informative prior), it was evident that the exponential function derived from the KM + exponential

parametric function still provided the most conservative estimate of the INV PFS (see the Bayesian parametric analysis in Appendix O.1.4).

Thus, KM data from GLOW were used for the first 15 cycles to capture early events followed by an exponential distribution as the base case.

In the base case, extrapolations are capped by GPM. Since the FCR-unsuitable population may have higher mortality than the general population, a standardised mortality ratio (SMR) adjustment to capture the excess mortality was tested as a scenario analysis. This is similar to the previous approach with direct extrapolation, but the projections are capped by a GPM curve adjusted for the excess mortality through a SMR (shown in Appendix O.2 with and without the application of excess mortality).

O-Clb PFS

The observed INV-assessed PFS data from the GLOW trial (70) at the extended follow up of median 34.1 months (KM shown in Figure 24) was used to estimate extrapolations of PFS 1L for O-Clb.

From visual inspection of the observed data (Figure 24), there is a marked drop in the PFS of the O-Clb arm at around 15 months. This sharp drop can be attributed to PFS events that perhaps occurred earlier but were only captured at the protocol-specified mandatory imaging timepoints. There is a window of time (between 9 and 15 months) when imaging was not mandatory which likely resulted in a high number of progression events captured at 15 months.

Appendix O.1.2 shows the standard parametric functions fitted to the O-Clb PFS arm from GLOW. Since the standard parametric distributions did not capture the underlying hazards of O-Clb PFS, flexible parametric survival analyses (spline modelling) were conducted and considered to be the base case for O-Clb PFS extrapolations. Flexible parametric survival analyses allowed increased complexity to capture the irregular hazard shape due to the steep drop observed at around 15 months (Figure 24).

Flexible parametric survival analyses were conducted in the log cumulative hazard, log cumulative odds, and inverse normal scales. All of these models provided similar fit to

the observed data and had comparable median survival. However, the hazard scale models were given preference over the models in odds and inverse normal scales because the latter two had considerably longer tails making the hazard scale models the most conservative choice.

The independently fitted extrapolations were assessed based on statistical goodness of fit, a comparison of observed vs. predicted, and clinical plausibility.

Table 39 presents a summary of the goodness-of-fit statistics for the INV PFS endpoint of O-Clb from GLOW.

Table 39 Statistical goodness-of-fit indicators (AIC/BIC) values for the independent parametric models fitted to INV PFS data for O-Clb

# of knots	AIC	BIC	Median PFS without capping (years)
1	223.41	228.71	[redacted]
2	219.45	227.42	[redacted]
3	218.02	228.63	[redacted]
4	202.16	215.43	[redacted]
5	200.43	216.35	[redacted]
6	NA*	NA	[redacted]
7 (base case)	180.42	201.65	[redacted]

AIC = Akaike information criteria; BIC = Bayesian information criteria; NA = not applicable; PFS = progression-free survival
*NA indicates the model did not converge

Models with 3 or more knots produced good and similar fit to the observed KM data, except for the steep drop when many progression events were observed, regardless of the number of knots. However, the fits produced considerably better results than those using standard parametric survival fits.

The best fitting model based on AIC and BIC was the model using 7 knots due to the projection cutting the steep drop at the centre. Among all candidate models from the flexible parametric analyses, the model with 7 knots was the one which provided the best fit to the observed INV PFS, and thus can be considered the best fitting model.

Figure 27 PFS extrapolations of O-Clb capped by GPM

1L = first line; GPM = general population mortality; KM = Kaplan-Meier; O-Clb = obinutuzumab + chlorambucil; PFS = progression-free survival

The 7 knot spline model fit the observed data well and produces long-term estimates that align with clinical opinion from the advisory board of clinical and health economic experts conducted in March 2022.(4) The Weibull was recommended as a reasonable long-term extrapolation and the graph shows the consistency between the 7 knot spline model and the Weibull in the long term. This was validated against the PFS estimates of the O-Clb arm from ELEVATE-TN(93) that has a similar dosing and reports a PFS of 25% at 4-years. In scenario analyses, other more optimistic scenarios are explored.

Table 40 Landmark estimates for the O-Clb INV PFS data from GLOW when capped by the UK GPM hazard

Distribution	6-month	1-year	2-year	4-year	5-year	10-year	15-year	20-year	30-year
7 knot spline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
External data	ELEVATE-TN O-Clb arm: 25% at 4 years (93); CLL14 O-Clb arm: 35.4% at 4 years(53)								

CLL = chronic lymphocytic leukaemia; O-Clb = obinutuzumab + chlorambucil

VenO and acalabrutinib PFS

Base case: HRs from anchored MAIC applied to the I+V exponential distribution (without KM); I+V vs. VenO (GLOW and CLL14) and I+V vs. acalabrutinib (GLOW and ELEVATE-TN) (Table 36)

The HRs from anchored MAICs (described in B.2.9 Indirect and mixed treatment comparisons) were used to estimate the PFS for VenO and acalabrutinib by applying these to the I+V reference curve (exponential without the first 15 cycles of KM). The base case used a HR in which I+V from GLOW was matched on inclusion/exclusion criteria and further adjusted based on age, ECOG, CIRS and TP53 mutation status to the comparator trial VenO or acalabrutinib arm. Clinical expert feedback sought in May 2022 validated the use of a single HR approach as the base case analysis.(5)

Adjusting for all available treatment effect modifiers was explored in a scenario analysis. A time-varying analysis matched on the same treatment effect modifiers as the base case was also explored as a scenario analysis given that there was evidence suggesting that the PH assumption was violated in all three trials (GLOW, CLL14 and ELEVATE-TN) for PFS. In addition, another scenario was conducted where VenO and acalabrutinib was assumed to be equivalent to I+V in the first 12 months, followed by using the base case HR (I+V vs. VenO = [redacted]; I+V vs. acalabrutinib = [redacted]) after 12 months.

Table 41 Anchored MAIC of I+V vs. VenO and acalabrutinib PFS

	I+V vs. VenO		I+V vs. acalabrutinib		
Model	**N(N_{eff})**	**HR [95%CI]**	**N(N_{eff})**	**HR [95%CI]**	**Scenario**
Single HR					
Adjusted for age, ECOG, CIRS, and TP53 mutation	174 (118)	[redacted]	211 (127)	[redacted]	Base case
Adjusted for all	136 (70)	[redacted]	154 (69)	[redacted]	Scenario 1
Unadjusted	211	[redacted]	211	[redacted]	Scenario 2
Time varying HR					
Model	**Period**	**HR [95%CI]**	**Period**	**HR [95%CI]**	**Scenario**
Adjusted MAIC analysis	≤12m	[redacted]	≤12m	[redacted]	Scenario 3
	>12m	[redacted]	>12m	[redacted]	
Assumption + single HR	≤12m	[redacted]	≤12m	[redacted]	Scenario 4
	>12m	[redacted]	>12m	[redacted]	

CI = confidence interval; CIRS = Cumulative Illness Rating Scale; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ; I+V = ibrutinib + venetoclax; MAIC = matching-adjusted indirect comparison; VenO = venetoclax + obinutuzumab; *Used in economic modelling

Figure 28 shows the resulting PFS estimations for I+V, VenO, and acalabrutinib monotherapy capped by GPM.

Figure 28 Comparison of PFS extrapolations for model comparators (using exponential extrapolation for I+V) capped by GPM

GPM = general population mortality; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; PFS = progression-free survival; VenO = venetoclax + obinutuzumab

Comparison of PFS extrapolations for model comparators (using exponential extrapolation for I+V) and a time-varying HR for external comparators is presented in Appendix Q.

Table 42 shows the PFS estimates capped by GPM for I+V, VenO, and acalabrutinib (assuming I+V is exponential).

Table 42 Landmark INV PFS estimates for model comparators when capped by the UK GPM hazard

Distribution	6 month	1-year	2-year	5-year	10-year	15-year	20-year	30-year
I+V	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VenO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RESONATE-2 (6)	PFS was 59% for ibrutinib at 7 years(6)							
CLL14	VenO PFS at 3 years: 81.9%; VenO PFS at 5 years: 51.4%							
ELEVATE TN NICE TA689 (2)	Acalabrutinib PFS at 3 years: 84.8%; Acalabrutinib PFS at ~5 years: 75.5% PFS landmark rate of 70% at 5 years with acalabrutinib was acceptable							

CLL = chronic lymphocytic leukaemia; I+V = ibrutinib + venetoclax; NICE = National Institute for Health and Care Excellence; PFS = progression-free survival; TA = technology appraisal; VenO = venetoclax + obinutuzumab

The NICE appraisal of acalabrutinib monotherapy (TA689)(2) noted that clinical experts suggested a landmark PFS estimate of 70% at 5 years with BTKi. This is in line with the acalabrutinib projection in the model which estimates a PFS of [redacted] at the 5-year mark.

PF 1L to Death

Base case: KM data for first 15 cycles, and annual mortality based on O-Clb arm from GLOW and constrained by GPM. Annual mortality based on O-Clb arm from GLOW and constrained by GPM for other comparators

Reference curve

To separate the deaths and progression events from the composite endpoint of PFS, pre-progression deaths observed in the GLOW trial were used to estimate the annual mortality rate. The annualised mortality rate derived from GLOW is converted to a transition probability from PF to death and was assumed to be a constant probability per cycle throughout the model horizon. In order to capture the early events of the I+V arm in the GLOW trial, the pre-progression mortality KM data was used to model the first 15 cycles. Since there was only one pre-progression death event beyond 15 cycles in the I+V arm, the annual mortality rate of the I+V arm was assumed to be the same as the observed annual mortality rate of the O-Clb arm. This enables the model to account for the early events within the first 15 cycles of treatment in the I+V arm and assume a conservative annual mortality rate beyond the 15-cycle period.

In order to ensure logical consistency, the transition probabilities are capped by age and gender adjusted GPM rate. Figure 29 shows the pre-progression mortality of the I+V and O-Clb arms compared to the GPM. The observed pre-progression mortality in the O-Clb arm is capped by the GPM (dotted curve) from the very beginning; the I+V arm, however, uses the observed pre-progression data in the first 15 cycles followed by using the pre-progression mortality from the O-Clb arm capped by GPM beyond 15 cycles.

Table 43 shows the annual mortality rate in PFS for the I+V and O-Clb arms based on total follow-up days and number of death events occurring during PFS in GLOW.

Table 43 Annual mortality rate in PFS derived from GLOW

Treatment	Total PFS Patient Years	Total PFS Death	Annual mortality rate in PFS
I+V	[redacted]	[redacted]	KM data for first 15 cycles; [redacted] after 15 cycles based on the O-Clb annual mortality
O-Clb	[redacted]	[redacted]	[redacted]

I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; NA = not applicable; O-Clb = obinutuzumab + chlorambucil; PFS = progression-free survival

Relative treatment effects for PFS 2L

Due to the lack of available comparative efficacy data, pre-progression mortality for VenO and acalabrutinib was assumed to be the same as O-Clb. Head-to-head data for VenO and acalabrutinib vs. O-Clb in their respective trials (CLL14 and ELEVATE-TN) has shown overall similar OS, thereby supporting the assumption made.

Figure 29 Pre-progression mortality observed in the GLOW trial vs. GPM

1L = first line; GPM = general population mortality; I+V = ibrutinib + venetoclax; O-Clb = Obinutuzumab + chlorambucil

Post progression transitions (PF 2L to PPS, PF 2L to Death, PPS to Death)

Modelling of the post progression transitions follows the same methodology used in the FCR-suitable population, as summarised in Table 44.

Table 44 Summary of clinical parameters for the post progression transitions

	Applicable to?	Approach	Data source	Link to section
PF 2L to PPS	All treatments irrespective of the second-line treatment composition†	Independent extrapolation of ibrutinib arm PFS; Assume same efficacy for all treatments	RESONATE trial Ibrutinib arm (1-2 prior line subgroup) for all treatments	PF 2L to PPS
PF 2L to Death	All treatments irrespective of the second-line treatment composition†	Annual mortality rate converted to a constant probability of death per cycle capped by GPM; Assume same efficacy for all treatments		PF 2L to Death
PPS to death	All treatments			PPS to Death

2L = second line; GPM = general population mortality; PF = progression-free; PPS = post-progression survival
† Second-line treatment comprises of a basket of acalabrutinib, VenR, and ibrutinib

B.3.3.4 High-risk population

Base case: Efficacy in high-risk patients is assumed equivalent to efficacy in FCR-unsuitable patients due to lack of data in high-risk patients. Ibrutinib and acalabrutinib are assumed to have the same efficacy based on TA689.(2)

Data available to directly inform clinical parameters for the high-risk population (del17p/TP53 mutation) were based on small patient sizes and would therefore provide unreliable estimates. Thus, the clinical inputs for the high-risk population are assumed to be the same as for the FCR-unsuitable population (described in B.3.3.3 FCR-unsuitable population) because the high-risk population has a similarly poor prognosis as that of the FCR-unsuitable population. This assumption was used and accepted in TA689,(2) where clinical experts explained that it was reasonable to assume a similar treatment effect of acalabrutinib for the populations with untreated CLL whether or not they had high-risk CLL. In addition, Janssen sought clinical advice regarding the robustness of this approach and this assumption was validated by clinical expert opinion.(5) Table 45 provides a summary of the clinical parameters used for the high-risk population in the model.

For ibrutinib monotherapy (which was not a comparator in the FCR-unsuitable population), the clinical inputs were assumed to be equivalent to acalabrutinib, another treat to progression BTKi therapy; NICE and clinicians agreed with this assumption in TA689.(2) The RESONATE-2 trial (6) analysed the efficacy of continuous ibrutinib use in a first-line setting with up to 8 years of follow-up. However, the trial is not representative of the high-risk population as it excluded patients with del17p and only 9% (11 of 124) of patients receiving ibrutinib had the presence of a TP53 mutation at baseline.

Table 45 Summary of clinical parameters for the high-risk population

Transition	Treatment	Approach	Data source	Link to section
PF 1L to PF 2L or PPS	I+V	Use KM data for the first 15 cycles; Independent extrapolation of I+V (exponential fitting)	I+V GLOW PFS (34.1m follow up)	PF 1L to PF 2L or PPS
	VenO	MAIC between the I+V arm (GLOW) and the VenO arm (CLL14)	VenO CLL14 PFS (28m follow up)	
	Acalabrutinib and ibrutinib	MAIC between the I+V arm (GLOW) and the acalabrutinib arm (ELEVATE-TN)	Acalabrutinib ELEVATE-TN PFS (28.3m follow up)	
PF 1L to death	I+V	Use KM data for the first 15 cycles; followed by assuming a constant probability of death capped by GPM	I+V GLOW PFS (34.1m follow up) O-Clb GLOW PFS beyond 15 cycles	PF 1L to Death†
	VenO, acalabrutinib, and ibrutinib	Constant probability of death capped by GPM	O-Clb GLOW PFS	
PF 2L to PPS	All treatments irrespective of the second-line treatment composition†	Independent extrapolation of ibrutinib arm PFS; Assume same	RESONATE trial Ibrutinib arm (1-2 prior line subgroup)	Post progression transitions (PF 2L to PPS, PF 2L to

Transition	Treatment	Approach	Data source	Link to section
		efficacy for all treatments		Death, PPS to Death)
PF 2L to Death	All treatments	Annual mortality rate converted to a constant probability of death per cycle capped by GPM; Assume same efficacy for all treatments		
PPS to death				

1L = first line; 2L = second line; CLL = chronic lymphocytic leukaemia; GPM = general population mortality; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; MAIC = matching adjusted indirect treatment comparisons; O-Clb = obinutuzumab + chlorambucil; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; VenO = venetoclax + obinutuzumab

† O-Clb is a relevant comparator in the FCR-unsuitable without del17p population, but is not applicable to the high-risk population.

ᵀ Second-line treatment comprises of a basket of acalabrutinib, VenR, and ibrutinib

B.3.4 Measurement and valuation of health effects

As previously described in B.1.3.1 Disease overview, CLL is generally an incurable disease and is life-threatening due to the development of immune cytopenias and impaired production of normal immunoglobulin.(20, 26, 27) The clinical manifestations and consequences of CLL can have a substantial negative impact on patients' QoL as a result of disease-related symptoms (such as fatigue, recurrent infections and anaemia); treatment-related AEs; and the psychological, socioeconomic and functional effects of living with the disease.(16, 17) Certain aspects of available CLL treatment regimens (such as treatment duration and administration route) can impact patient QoL, and unmet needs persist in terms of treatment options for FCR-suitable, FCR-unsuitable, and high-risk populations, as described in B.1.3.4 Unmet need.

In order to demonstrate the potential impact of treatment on patient QoL, the cost-effectiveness model for all three populations accounts for the following:

- HRQoL measurements tied to the PF, PF2L, PPS health states
- Disutilities associated with treatment-related AEs in the first-line setting
- Disutilities associated with IV treatment administration

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

The CAPTIVATE trial did not include collection of HRQoL using EQ-5D in the FCR-suitable population. The GLOW trial collected HRQoL data using the EQ-5D-5L health questionnaire in the FCR-unsuitable population.(72) The EQ-5D-5L is a five-item questionnaire that assesses five domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analogue scale (VAS) rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the five separate questions are categorical and cannot be analysed as cardinal numbers. However, the scores for the five dimensions are used to compute a single country-specific utility score where a value of 0 is equivalent to death, negative values represent a health status worse than death and 1 is equivalent to a perfect health state.

Patient-reported outcomes (PRO) assessments in GLOW were to be completed prior to any clinical tests, procedures or other consultations that would influence a patient's perceptions of their current health state.(72) The EQ-5D-5L questionnaire was administered at the following visits per the GLOW clinical trial protocol:(72)

- Day 1 of Cycles 1, 3 and 5 (i.e., every 8 weeks for the first 6 months)
- Every 12 weeks after Cycle 5 prior to disease progression
- At end-of-treatment (30 days after the last dose)
- At the first two post-treatment, post-PD visits (every 24 weeks)

HRQoL data were not captured in the FD cohort of the CAPTIVATE trial.(68)

Mapping and analysis methods

<u>Deriving health utility scores</u>

The NICE methods recommend EQ-5D-5L to be mapped onto EQ-5D-3L if possible. In order to map the EQ-5D-5L data collected in the GLOW trial to the EQ-5D-3L, a mapping algorithm developed by the DSU was applied using the "EEPRU dataset,"(99) which provides age- and sex-adjusted UK utility values.

Missing data

The analyses of health utility data from GLOW excluded EQ-5D values that were collected after the censoring date for PFS because the progression status of the patient could not be confirmed (i.e., it was unknown whether patients were still progression-free during these post-censoring assessments).

Additionally, any missing EQ-5D values were removed from the analyses, with no imputation performed for missing utility data.

Descriptive analyses

The number of EQ-5D observations with non-missing utility values and the distribution of observed utility values (i.e., mean, mean standard error, SD, median, interquartile range, minimum and maximum) were summarised by scheduled visits and by treatment arm in the GLOW trial. Observations that were not mapped to any scheduled visit were not considered.

Pre- and post-progression utility

Pre- and post-progression utility was defined as the average utility for patients before and after the date of progression based on a computerised algorithm. Average utility was calculated using a repeated-measures linear mixed-effects (RMME) model. A subject random intercept was used to account for repeated measures of individuals over multiple cycles before progression. An autoregressive covariance structure was used, given that other covariance structures demonstrated convergence issues. The covariates used to identify utility increment were those considered relevant to the economic model: baseline utility and progression status (per investigator); these covariates were kept in the model regardless of statistical significance.

Summary of results

Descriptive statistics of utility over scheduled visits in GLOW are presented in Appendix R.1. At baseline, the O-Clb arm had a slightly higher mean utility score compared to the I+V arm, but there was not a clear trend over time as seen in Figure 30. The

overlapping standard error bars at most visits suggests that there was no statistically significant treatment effect.

Post-progression PROs were only collected for two visits. Across the post-progression follow-up visits, the mean utility score was higher with I+V than with O-Clb. However, available data were considerably more limited (few patients with information available) in the post-progression phase than in the pre-progression phase, particularly in the I+V arm. It must be noted that post-progression utility estimates do not consider differences in time to progression.

Figure 30 EQ-5D-3L Utility Score Over Scheduled Visits in GLOW

DE = disease evaluation; PD = progressive disease; UK = United Kingdom

For the pre- and post-progression utility analyses, there were a total of 1,723 pre-progression and 51 post-progression EQ-5D observations contributing to the analytical dataset. Table 46 shows the pre- and post-progression utility for both treatment arms combined (I+V and O-Clb) based on the RMME model. The results of the RMME model are presented in Appendix R.2.

Table 46 Pre- and post-progression utility derived from the GLOW trial using the RMME model

	Estimate	Lower 95% CI	Upper 95% CI	SE	p-value
PF 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Progressed Disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1L = first line; CI = confidence interval; PF = progression free; SE = standard error

The pre-progression utility observed in the GLOW trial exceeded the mean age-adjusted utility of the UK population derived from the Health Survey for England (HSE) 2014 data set (recommended by the NICE DSU report 2022).(99) However, the utility observed was within the 95% CI of the similar age-adjusted general population in the UK as reported by Ara and Brazier 2011.(100) Table 47 presents the PF utility derived from the GLOW trial and the corresponding age-adjusted utility of the UK general population from the two sources.

Table 47 Pre-progression utility from GLOW vs. age-adjusted general population utility

Health condition	Estimate	Lower 95% CI	Upper 95% CI	Source
PF 1L	[redacted]	[redacted]	[redacted]	GLOW
No history of health condition: 'cancer'; age band: 65 to ≤70 years	0.808	0.794	0.821	Ara and Brazier 2011(100)
General population UK (age = 71; male = 57.8%)	0.798	NA	NA	HSE 2014(99)

1L = first line; CI = confidence interval; HSE = Health Survey for England; NA = not applicable; PF = progression-free; UK = United Kingdom

The PF utility derived from GLOW is justifiable based on the following:

- High PF utility values that exceed the corresponding general population utility are consistent in PF utilities derived from other comparator trials [VenO(1); acalabrutinib monotherapy(2)]. The high PF utility value derived from GLOW is unlikely to be an issue with sampling or selection bias as the clinical trials had different designs but yielded similar PF utilities.
- The PF utility may be attributed to the fact that patients may be experiencing relief from symptoms compared to how they were feeling prior to receiving first-line treatment.

The EQ-5D-3L utility mapped from the EQ-5D-5L utility observed in the GLOW trial for patients with PD is generally higher than the PD utilities used by prior models in previously untreated CLL. This could be due to two reasons:

- There was a low number of EQ-5D observations with PD in the combined I+V and O-Clb arms of the GLOW trial (N=51 of 1,774).
- Progression events in the GLOW trial were determined by CT scanning, which results in patients being classified as having progressed disease in the clinical trial even when they are not symptomatic; this leads to a similar utility value for both PD and PF.

B.3.4.2 Health-related quality-of-life studies

An SLR was conducted to identify studies, published between 2013 and 2022, assessing the HRQoL of patients with previously untreated CLL.

The review identified 21 studies in the FCR-suitable and -unsuitable patients. Eight of the 21 included studies were clinical trials, four were observational studies and nine related to previous HTA submissions. Overall, the four observational studies and nine HTA submissions used a UK healthcare perspective. EQ-5D was the most frequently used tool for measurement of QoL (n=4). The remaining studies had limited relevance to decision-making in the UK and so were excluded from further consideration (conducted from a multi-country/global perspective with no specification of the included individual countries, did not report the geographic location, conducted in Australia)

Four studies were identified which carried out analysis for patients with del17p/TP53 mutation. These publications had a UK perspective and were previously published HTA submissions. The SMC 2020(101) submission for VenO derived utility data from previously published UK HTA submissions for its cost-effectiveness analysis. The utility values were captured for pre-progression and post-progression health states. The post-progression utility implemented was 0.6. The pre-progression utilities in SMC 2020(101) varied by type of therapy (IV or oral) and the off-treatment period. The NICE TA663(1) and NICE TA429(64) submissions for VenO and ibrutinib derived utility values from previously published HTA publications and the RESONATE trial, respectively, for their

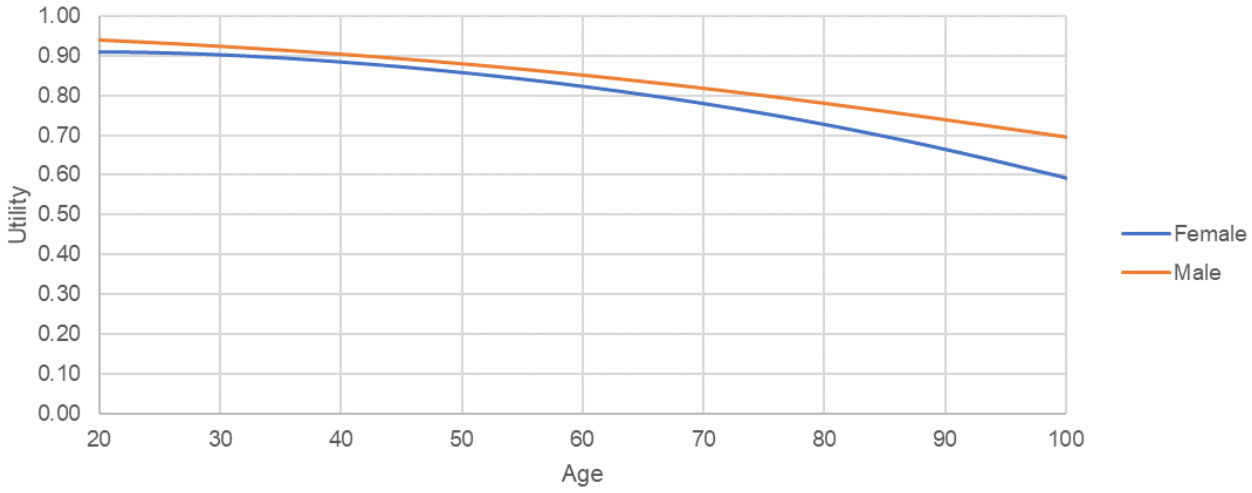
cost-effectiveness analysis. These submissions included utility values for PFS and PPS health states and also utility decrement associated with AEs.

Only those studies which report results for I+V or the comparators of interest and a UK perspective were extracted. Full details of the SLR search strategy, methodology and results are presented in Appendix H.

B.3.4.3 Age-based utility decrement

Age-adjusted utility values were implemented in the model to account for the expected decrease over time in QoL associated with aging. The utility estimates for each model cycle were adjusted based on the difference between patients' mean age during the current cycle and the mean age at baseline. The mean age at baseline in the GLOW study was 71 years which was used as the starting age for the FCR-unsuitable population in the model. The age-adjusted utilities were implemented using the mean EQ-5D-3L values by age estimated from the latest available wave of the HSE that included the EQ-5D-3L (published in 2014; Figure 31).(99)

Figure 31 EQ-5D-3L by age and gender in the UK, HSE 2014



A proportional age adjustment factor for each year was calculated based on the mean utility at the measured age (e.g., the measured age for the PF utility from GLOW is 71 based on the median age of patients) and the corresponding age-adjusted utility in every year. The age adjustment was applied to the mean utility in a multiplicative

fashion in each cycle of the model. The mean utility estimates stratified by age and gender derived from HSE 2014 is presented in Appendix R.3. Additionally, Appendix R.4 shows the reference age of the PF and PD health states, stratified by the population.

B.3.4.4 Adverse events

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

The model accounts for the HRQoL impact of grade ≥3 AEs that occurred in at least 5% of patients treated with I+V or one of the comparators. Cardiac events (cardiac failure, myocardial infarction and atrial fibrillation) were included where reported irrespective of their incidence as patients receiving I+V may experience cardiotoxicity. The incidence of AEs that met the selection criteria for the FCR-suitable population, the FCR-unsuitable, and the high-risk is presented in Table 48, Table 49 and Table 50.

Table 48 Incidence of grade ≥3 AEs considered in the FCR-suitable population

AE, %	I+V(68)	FCR(83)
Anaemia	[redacted]	15.8%
Atrial fibrillation	1.3%	0.0%
Cardiac failure	[redacted]	0.0%
Hypertension	5.7%	1.9%
Leukocytopenia/Leukocytosis/White blood cell decreased	[redacted]	41.1%
Lymphocyte count decreased	[redacted]	65.2%
Lymphocyte count increased	[redacted]	13.9%
Neutropenia/Febrile neutropenia/Neutrophil count decreased	[redacted]	45.6%
Thrombocytopenia/Platelet count decreased	[redacted]	16.5%

AE = adverse event; FCR = fludarabine + cyclophosphamide + rituximab; I+V = ibrutinib + venetoclax

Table 49 Incidence of grade ≥3 AEs considered in the FCR-unsuitable population

AE, %	I+V(70)	O-Clb(70)	VenO(85)	Acalabrutinib(93)
Anaemia	[redacted]	[redacted]	8.0%	0.0%
Atrial fibrillation	6.6%	0.0%	1.9%	1.1%
Cardiac failure	3.8%	0.0%	1.9%	0.0%
Diarrhoea	10.4%	1.0%	3.8%	0.6%
Hypertension	7.5%	1.9%	3.3%	2.8%
Hyponatremia	5.7%	0.0%	0.0%	0.0%
Infections	[redacted]	[redacted]	0.0%	16.2%
Infusion related reaction	0.0%	[redacted]	9.0%	0.0%
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	0.0%	0.0%
Myocardial Infarction	[redacted]	[redacted]	1.9%	0.0%
Neutropenia/Febrile Neutropenia/Neutrophil count decreased	[redacted]	[redacted]	62.3%	11.2%

AE, %	I+V(70)	O-Clb(70)	VenO(85)	Acalabrutinib(93)
Pneumonia	6.6%	5.7%	5.7%	0.0%
Thrombocytopenia/Platelet count decreased	5.7%	20.0%	15.6%	0.0%

AE = adverse event; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab

Table 50 Incidence of grade ≥3 AEs considered in the high-risk population

AE, %	I+V(70)	VenO(85)	Acalabrutinib (93)	Ibrutinib(102)
Anaemia	[redacted]	8.0%	0.0%	7.4%
Atrial fibrillation	6.6%	1.9%	1.1%	5.2%
Cardiac failure	3.8%	1.9%	0.0%	0.0%
Cataract	[redacted]	0.0%	0.0%	5.2%
Diarrhoea	10.4%	3.8%	0.6%	4.4%
Hypertension	7.5%	3.3%	2.8%	8.1%
Hyponatremia	5.7%	0.0%	0.0%	5.9%
Infections	[redacted]	0.0%	16.2%	0.0%
Infusion related reaction	0.0%	9.0%	0.0%	0.0%
Musculoskeletal and connective tissue disorders	[redacted]	0.0%	0.0%	0.0%
Myocardial Infarction	[redacted]	1.9%	0.0%	0.0%
Neutropenia/Febrile Neutropenia/Neutrophil count decreased	[redacted]	62.3%	11.2%	12.6%
Pneumonia	6.6%	5.7%	0.0%	11.9%
Thrombocytopenia/Platelet count decreased	5.7%	15.6%	0.0%	0.0%

AE = adverse event; I+V = ibrutinib + venetoclax; VenO = venetoclax + obinutuzumab

For each AE, the associated disutility and duration are applied to the proportion of patients who experience the event as a one-off at the beginning of the model. This approach is consistent with prior NICE TAs in CLL.(1, 2) Table 51 shows the disutility associated with each AE and the corresponding duration, which were sourced from prior NICE TAs and other literature.

Table 51 Disutility and duration estimates for AEs

AE	Disutility	Source	Duration (days)	Source
Anaemia	-0.09	(87)	23.21	(87)
Diarrhoea	-0.20	(62)	3	(103)
Infections	-0.22	(104)	14	Assumption
Infusion related reaction	-0.20	(87)	3.5	(87)
Leukocytopenia/ Leukocytosis/White blood cell decreased	-0.16	Assumed to be the same as Neutropenia	15.09	Assumed to be the same as Neutropenia
Lymphocyte count decreased	-0.16		15.09	
Lymphocyte count increased	-0.16		15.09	
Neutropenia/Febrile Neutropenia/Neutrophil count decreased	-0.16	(87)	15.09	(87)
Pneumonia	-0.195	(105)	18.21	(62)
Thrombocytopenia/Platelet count decreased	-0.11	(87)	23.21	(87)
Atrial fibrillation	-0.22	No data; assumed to be the same as highest disutility (infection)	14	No data; assumed to be the same as highest disutility (infection)
Cardiac failure	-0.22		14	
Cataract	-0.22		14	Assumption
Hypertension	-0.22		14	Assumption
Hyponatraemia	-0.22		14	Assumption
Musculoskeletal and connective tissue disorders	-0.22		14	Assumption
Myocardial Infarction	-0.22		14	Assumption

AE = adverse event

It is assumed that the baseline utility value for progression-free patients (derived from the GLOW trial) does not account for AEs that patients experience while they are progression-free. AE disutilities are applied separately in the model.

A similar approach as described above for AE disutilities is used to model the cost associated with AEs (described in B.3.5.2 AE management cost).

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

The CAPTIVATE trial did not evaluate HRQoL. Hence, the PF utility from the GLOW trial informed the PF utility of the FCR-suitable population in the model, with a relative utility multiplier to adjust for the younger age of the FCR-suitable population (median age of 59 years in CAPTIVATE) compared to the GLOW trial (median age of 71 years). The age adjustment utility multiplier was based on the general population utility values derived from HSE 2014.(99)

The utility derived from the GLOW trial for the PD health state (applicable to the 2L PF and PPS health states) is higher than that used by prior models in previously untreated CLL (due to the low number of progression events and the use of CT scanning to determine progression events); thus, external data were used to inform the utility associated with the PD health state. A PD utility of 0.6 derived from Holzner et al.(106) was used for the post progression states (2L PF and PPS), in line with prior NICE TAs in CLL.(1, 2, 62, 87, 107, 108)

In addition, a utility decrement associated with IV administration was included in the model based on TA343 (obinutuzumab NICE appraisal).(58) This utility decrement was attributed in an additive fashion for each IV administration in a cycle. For instance, patients receiving obinutuzumab experience an IV disutility three times in cycle 1 (once on day 1, day 8, and day 15) and one time each in cycles 2 through 6 (once on day 1 of each cycle). If multiple treatments in a regimen are administered via IV infusion, IV disutilities are added separately for individual components to derive the disutility associated with the regimen.

Table 52 Summary of utility values for cost-effectiveness analysis, FCR-suitable population

State	Utility value: mean (SE)	95% CI
PF 1L	[redacted]	[redacted]
PF 2L	[redacted]	[redacted]
Post 2L progression	[redacted]	[redacted]

State	Utility value: mean (SE)	95% CI
Utility decrement due to IV treatment	[redacted]	[redacted]

*Derived from the utility from GLOW trial subject to age adjustment to match the starting age of the FCR-suitable population; † SE was assumed to be the same as utility derived from GLOW; † Utility in PF 2L and Post progression were derived from external data subject to age adjustment to match the starting age of the FCR-suitable population
1L = first line; 2L = second line; CI = confidence interval; IV = intravenous; PF = progression free; SE = standard error

The base case analysis of the FCR-unsuitable population used the EQ-5D-3L utility value derived from the GLOW study for the PF health state. This approach aligns with NICE recommendations by utilising the HRQoL estimates derived from the clinical trial.

Table 53 Summary of utility values for cost-effectiveness analysis, FCR-unsuitable population

State	Utility value: mean (SE)	95% CI
PF 1L	[redacted]	[redacted]
PF 2L	[redacted]	[redacted]
Post 2L progression	[redacted]	[redacted]
Utility decrement due to IV treatment	[redacted]	[redacted]

1L = first line; 2L = second line; CI = confidence interval; IV = intravenous; PF = progression free; SE = standard error; † Utility in PF 2L and Post progression were derived from external data subject to age adjustment to match the starting age of the FCR-suitable population

The utility values for the high-risk population were assumed to be the same as the FCR-unsuitable population due to a paucity of specific data to inform HRQoL in this patient population (Table 53).

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The model incorporated the following types of costs (refer to Appendix I for details on the identification of relevant cost and healthcare resource data for the model) in line with NICE guidance.

Table 54 Summary of key cost input categories and data sources

Cost category	Source	Key features	Justification
Treatment-related costs			
Drug acquisition	BNF, eMIT	Dosing regimen derived from the SmPCs; eMIT was used to derive the cost of generic treatments	Aligned with the NICE guidance
Drug administration	NHS reference costs 2019-2020	Oral therapies do not incur an administration cost	Aligned with NICE guidance and prior NICE TAs(1, 2)
Subsequent treatment	Acquisition: BNF, eMIT Administration: NHS reference costs 2019-2020	Dosing regimen derived from the SmPCs; eMIT was used to derive the cost of generic treatments; Subsequent treatment composition is derived from an advisory board of clinical and health economic experts advisory board conducted in March 2022(4)	Aligned with the NICE guidance
AE management	NHS reference costs 2019-2020	One-off cost	Aligned with NICE guidance and prior NICE TAs(1, 2)
TLS management	Prior NICE TAs	One-off cost	Aligned with prior NICE TAs(1)
Disease management costs			
Disease management	NHS reference costs 2019-2020	Routine care cost applicable to PF 1L, PF 2L, and PPS health states. FCR-suitable population includes an additional component of G-CSF acquisition cost as concomitant medications	Aligned with the NICE guidance
End-of-life costs			
Terminal care cost	Published literature	One-off cost	Aligned with prior NICE TAs(1, 2)

1L = first line; 2L = second line; AE = adverse event; BNF = British National Formulary; eMIT = Electronic Market Information Tool; FCR = fludarabine, cyclophosphamide, rituximab; G-CSF = granulocyte colony-stimulating factor; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PF = progression free; PPS = post-progression survival; SmPC = summary of product characteristics; TA = technology appraisal; TLS = tumour lysis syndrome

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs in the model were calculated with information about dosing regimens (and patient characteristics pertinent to dosing). Dosing regimens of treatments under consideration for the FCR-suitable, FCR-unsuitable, and high-risk populations were derived from the corresponding SmPCs (Table 22, Table 23, Table 24).

Unit costs for treatments included in the cost-effectiveness analysis were collected from the British National Formulary (BNF), Monthly Index of Medical Specialities (MIMS) and electronic market information tool (eMIT); these are reported in Table 55. Where multiple pack prices were available, the model applied whichever price corresponded to the lowest cost per mg. A confidential patient access scheme (PAS) [redacted] for ibrutinib has been agreed with NHS England and the list price with the PAS applied is commercial-in-confidence. The acquisition cost of the rest of the treatments do not include any PASs; note that this includes venetoclax, so the actual cost-effectiveness of I+V could potentially be significantly superior to the ICERs reported in this document.

Table 55 Unit cost of therapies

Treatment	Strength	Units per pack	Cost per piece	Source
Ibrutinib	560.0 mg	28	[redacted]	MIMS Drug Database. Access date: February, 2022
Ibrutinib	420.0 mg	28		
Ibrutinib	280.0 mg	28		
Ibrutinib	140.0 mg	28		
Venetoclax	100.0 mg	112	£4,789.47	
Venetoclax	100.0 mg	14	£598.68	
Venetoclax	100.0 mg	7	£299.34	
Venetoclax	50.0 mg	7	£149.67	
Venetoclax	10.0 mg	14	£59.87	
Obinutuzumab	1,000.0 mg/ml	1.0 ml	£3,312.00	
Chlorambucil	2.0 mg	25	£27.01	
Acalabrutinib	100.0 mg	60	£5,059.00	
Rituximab	10.0 mg	50.0 ml	£785.84	
Rituximab	10.0 mg	10.0 ml	£157.17	
Fludarabine	50.0 mg	1	£20.28	Drugs and pharmaceutical eMIT; Pharmex data for the period 01/01/2021 -
Cyclophosphamide	2,000.0 mg	1	£27.50	
Cyclophosphamide	1,000.0 mg	1	£13.55	

Treatment	Strength	Units per pack	Cost per piece	Source
Cyclophosphamide	500.0 mg	1	£8.23	30/06/2021, for Pharmex products shown as Generic in the period 01/07/20 - 30/06/21

MIMS = Monthly Index of Medical Specialities; eMIT = electronic market information tool
†Includes the proportional, confidential discount applied to the list price of ibrutinib

The cost of treatments used in weight/body surface area (BSA)-based regimens is dependent on the corresponding patient characteristics. BSA and weight were derived separately for each population and are described in Table 56.

Table 56 Patient characteristics used in the economic analysis

Population	Weight, kg	Height, cm	BSA†, m^2	Source
FCR-suitable	88.3	177.39	2.06	Mean weight and height derived from E1912 trial (5)
FCR-unsuitable and high-risk populations	77.0	167.6	1.87	Mean weight and height derived from the GLOW trial (70)

BSA = body surface area; FCR = fludarabine, cyclophosphamide, rituximab
†BSA derived from Du-Bois method based on mean weight and height(109)

The model assumed slight dose reductions among treatment comparators, reflecting observed declines in dose intensity in clinical trials. It was assumed that the magnitude of these reductions (Table 57) could vary for each component of a treatment regimen, and that dose intensity impacts the drug cost, but not efficacy.

Table 57 Dosing intensity estimates

Population	Treatment	Component	Estimated dose intensity	Source
FCR-suitable population	I+V	Ibrutinib	[redacted]	CAPTIVATE - FD cohort (all patients); November 2021 CSR (68)
		Venetoclax		
	FCR	Fludarabine	94.3%	E1912 trial (83)
		Cyclophosphamide	94.3%	
		Rituximab	94.3%	

Population	Treatment	Component	Estimated dose intensity	Source
FCR-unsuitable and high-risk populations	I+V	Ibrutinib	[redacted]	GLOW trial; November 2021 CSR (70)
		Venetoclax		
	O-Clb†	Obinutuzumab		GLOW trial; November 2021 CSR (70)
		Chlorambucil		
	VenO	Venetoclax	100%	Assumption due to lack of data
		Obinutuzumab	100%	
	Acalabrutinib monotherapy	Acalabrutinib	99.2%	Median relative dose intensity; ELEVATE-TN (86)
	Ibrutinib monotherapy†	Ibrutinib	94.5%	RESONATE-2 (6)

CSR = clinical study report; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; I+V = Ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab
† Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population

Some proportion of an IV-based or oral drug may be wasted if perfect vial sharing is not practised or if full packages are not used, respectively. Wastage for IV drugs was considered in the base case, where the cost of IV drugs is calculated on a per-vial basis, rather than the mg infused. Oral drug wastage was not considered in the base case but explored as a scenario analysis.

The drug acquisition cost per cycle is estimated as a function of unit costs, the dosing intensity, dosing regimen and patient characteristics such as weight or BSA (if applicable). Estimated per-cycle costs employed in the model are summarised in Table 58.

Table 58 Drug acquisition cost per cycle

Treatment	Component	Cost per cycle (£)
FCR-suitable population		
I+V	Ibrutinib	[redacted] (Cycles 1 to 15)
	Venetoclax	£1,031.14 (Cycle 4) £4,458.97 (Cycles 5 to 15)
FCR	Fludarabine	£424.20 (Cycles 1-6)
	Cyclophosphamide	£79.90 (Cycles 1-6)
	Rituximab	£1,257.35 (Cycle 1) £1,571.69 (Cycles 2-6)

Treatment	Component	Cost per cycle (£)
FCR-unsuitable and high-risk populations		
I+V	Ibrutinib	[redacted] (Cycles 1 to 15)
	Venetoclax	£995.70 (Cycle 4) £4,305.73 (Cycles 5 to 15)
O-Clb†	Obinutuzumab	9,399.00 (Cycle 1) £3,312.00 (Cycles 2-6)
	Chlorambucil	£40.72 (Cycles 1-6)
VenO	Venetoclax	£59.87 (Cycle 1) £2,245.06 (Cycle 2) C3 to C15: £4,789.47 (Cycles 3 to 15)
	Obinutuzumab	£9,936.00 (Cycle 1) £3,312.00 (Cycles 2-6)
Acalabrutinib	Acalabrutinib	£4,683.96 (until progression)
Ibrutinib monotherapy†	Ibrutinib	[redacted] (until progression)

FCR = fludarabine + cyclophosphamide + rituximab; I+V = Ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab
† Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population; * Includes the confidential PAS discount for ibrutinib
mg = milligram; All cycles comprise of 28 days

Drug administration costs

Consistent with prior NICE TAs for first-line CLL,(1, 2) no administration costs were incurred for oral drugs, whereas drug administration costs for IV-administered therapies were based on NHS reference cost code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance). Table 59 presents a summary of drug administration costs employed in the model.

Table 59 Summary of drug related administration costs

Treatment	Component	Unit cost per administration (£)	Administrations per cycle	Cost per cycle (£)
FCR-suitable population				
I+V	Ibrutinib	0	28	0
	Venetoclax	0	28	0
FCR	Fludarabine	221.35	3	664.05
	Cyclo-phosphamide	221.35	3	664.05
	Rituximab	221.35	1	221.35
FCR-unsuitable and high-risk populations				
I+V	Ibrutinib	0	28	0
	Venetoclax	0	28	0

Treatment	Component	Unit cost per administration (£)	Administrations per cycle	Cost per cycle (£)
O-Clb†	Obinutuzumab	221.35	3 in cycle 1, followed by 1 per cycle up to cycle 6	664.05 in cycle 1; 221.35 in cycles 2-6
	Chlorambucil	0	2	0
VenO	Venetoclax	0	7 in cycle 1, followed by 28 per cycle up to cycle 12	0
	Obinutuzumab	221.35	3 in cycle 1, followed by 1 per cycle up to cycle 6	664.05 in cycle 1; 221.35 in cycles 2-6
Acalabrutinib	Acalabrutinib	0	56	0
Ibrutinib monotherapy†	Ibrutinib	0	28	0

FCR = fludarabine + cyclophosphamide + rituximab; I+V = Ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab
† Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population
All cycles comprise of 28 days

Subsequent treatment cost

Upon progressing from first-line treatment, patients are eligible for subsequent treatment. This is explicitly costed in the model by accounting for the distribution of treatments administered in the subsequent line of therapy, which can vary according to the treatment received in the first-line setting. The proportions of subsequent treatment were derived from UK clinical expert opinion (Table 60).(110)

Table 60 Subsequent treatment regimens by first-line treatment option

Population	First-line treatment	Subsequent treatment		
		Ibrutinib monotherapy	VenR	Acalabrutinib monotherapy
FCR-suitable	I+V	[redacted]	[redacted]	[redacted]
	FCR			
FCR-unsuitable and high-risk populations	I+V			
	O-Clb†			
	VenO			
	Acalabrutinib			
	Ibrutinib monotherapy†			

† Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population
FCR = fludarabine, cyclophosphamide, rituximab; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab

Drug acquisition

Drug acquisition costs associated with subsequent therapy were calculated as a weighted average of the per-cycle costs for each therapy, with the proportion of treatments presented in Table 60 serving as the weights. Per-cycle costs for each subsequent therapy were estimated based on their respective dosing regimens and unit costs, similar to the approach for first-line treatments (B.3.5.1 Drug acquisition costs).

Dosing regimens for subsequent therapies incorporated in the model are outlined in Table 61. Unit costs are consistent with the unit costs used in the first-line setting (Table 55).

Table 61 Dosing regimens of subsequent treatment used in the economic analysis

Treatment	Administration	Dosing Regimen	Source
Ibrutinib monotherapy	Oral	420 mg daily until progression	Imbruvica 420 mg film-coated tablets(13)
VenR	Venetoclax: Oral; Rituximab: IV	Venetoclax: 5-week ramp up (20-400 mg daily), followed by 400 mg daily up to cycle 28 Rituximab: 375 mg/m^2 on day 1 of cycle 3 followed by 500 mg/m^2 on day 2 of cycle 3, followed by 500 mg/m^2 daily up to cycle 8	Venclyxto 100 mg film-coated tablets(8)
Acalabrutinib	Oral	100 mg twice daily until progression	Calquence 100 mg hard capsules(61)

C = cycle; D = day; mg = milligram; IV = intravenous; VenR = venetoclax + rituximab; All cycles comprise of 28 days

Concordant with first-line therapy, the model assumed slight dose reductions during subsequent treatment that impacted drug acquisition costs but did not influence efficacy. Due to data limitations, it was assumed that dose intensity estimates (presented in Table 62) did not vary for FCR-suitable and FCR-unsuitable patients.

Table 62 Dosing intensity estimates for subsequent treatment

Treatment	Component	Estimated dose intensity	Source
Ibrutinib monotherapy	Ibrutinib	94.5%	RESONATE-2
VenR	Venetoclax	97%	TA561(108)
	Rituximab	97%	
Acalabrutinib	Acalabrutinib	99.2%	Median relative dose intensity from ELEVATE-TN(86)

VenR = venetoclax + rituximab

The cost per cycle applied in the analysis for treatments under consideration is presented in Table 63.

Table 63 Drug acquisition cost for subsequent treatment, per cycle

Subsequent treatment	Component	Cost per cycle (£)
Ibrutinib monotherapy	Ibrutinib	[redacted] until progression
VenR	Venetoclax	£58.07 cycle 1 £2,177.71 cycle 2 £4,645.79 up to cycle 28
	Rituximab	£2,671.87 cycle 3 £1,571.69 cycles 4-8
Acalabrutinib	Acalabrutinib	£4,683.96 until progression

* Includes the confidential PAS discount for ibrutinib
FCR = fludarabine + cyclophosphamide + rituximab; O-Clb = obinutuzumab + chlorambucil; VenR = venetoclax + rituximab

Drug administration

Concordant with first-line therapy (B.3.5.1 Drug administration costs), no administration costs were incurred for oral drugs when administered as part of subsequent treatment, whereas costs for IV-administered therapies were based on NHS reference cost code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance). A summary of drug-related administration costs associated with subsequent treatment is presented in Table 64.

Table 64 Drug administration cost for subsequent treatment, per cycle

Treatment	Component	Cost per Cycle (£)
Ibrutinib monotherapy	Ibrutinib	0
VenR	Venetoclax	0
	Rituximab	£443 cycle 3 £221 cycles 4-8
Acalabrutinib monotherapy	Acalabrutinib	0

VenR = venetoclax + rituximab

Duration of subsequent treatment

As noted previously (B.3.2.3 Model structure), accrual of costs attributable to subsequent therapy occurs only for as long as patients remain on treatment. This duration is modelled using second line PFS, as derived from the ibrutinib arm of the

RESONATE trial (1-2 lines of prior therapy). Equivalent efficacy is assumed across all 2L treatments.

Alternative measures, such as TTNT, were not used to model the time at which patients initiate subsequent treatment due to the differing definitions of TTNT used across the clinical trials of interest for VenO and acalabrutinib monotherapy (see Appendix N for definitions of TTNT).

The model base case incorporates a treatment-free interval (TFI) of 14 cycles derived from the ERG preferred base case of 14 cycles in TA689,(2) meaning that patients initiate subsequent treatment 14 cycles after progression on first-line therapy. Scenario analyses were conducted to explore the impact of varying TFI cycles on the results.

B.3.5.2 AE management cost

The costs of grade ≥3 AEs were included as one-off costs at the start of the model and were calculated as the product of their respective incidence rates (summarised in Table 48, Table 49 and Table 50 above) and unit costs.

The unit cost was a weighted average of the cost of treating patients for each AE in either inpatient or outpatient settings, with the likelihood of managing the event in each setting serving as the weights. The unit costs of managing AEs (presented in Table 65) were derived from the National Schedule of NHS costs (Year 2019-20).(111)

Table 65 Unit costs for AE management

AE	Cost (£)	Setting
Anaemia	371.65	Outpatient
Atrial fibrillation	1030.73	Inpatient
Cardiac failure	2,087.28	Inpatient
Cataract	2,111.56	Inpatient
Diarrhoea	574.39	Outpatient
Hypertension	651.08	Inpatient
Hyponatraemia	1,456.44	Inpatient
Infections	1,738.54	Inpatient
Infusion related reaction	1,855.49	Inpatient
Leukocytopenia/Leukocytosis/White blood cell decreased	1,533.37	Inpatient
Lymphocyte count decreased	1,533.37	Inpatient
Lymphocyte count increased	1,533.37	Inpatient

AE	Cost (£)	Setting
Musculoskeletal and connective tissue disorders	1,235.34	Inpatient
Myocardial infarction	1,592.17	Inpatient
Neutropenia/Febrile Neutropenia/Neutrophil count decreased	1,785.62	Inpatient
Pneumonia	1,908.16	Inpatient
Thrombocytopenia/Platelet count decreased	1,915.08	Inpatient

AE = adverse event

B.3.5.3 TLS management cost

TLS management costs consisted of one-off expenditures associated with prophylaxis for those at high risk of TLS and hospitalisation for those experiencing treatment-emergent TLS. Both venetoclax and obinutuzumab are associated with a risk of TLS, requiring prophylaxis and monitoring during initial treatment plus dose titration for venetoclax. The likelihood of patients requiring prophylaxis or hospitalisation for TLS was informed by GLOW and CLL14. TLS prophylaxis management was assumed to consist of IV hydration, blood chemistry monitoring, outpatient visits, hospital visits, and administration of anti-hyperuricemics, utilisation of which were derived from the venetoclax SmPC.(8) Unit costs for both TLS prophylaxis and hospitalisation were sourced from the National Schedule of NHS costs (Year 2019-20).(111)

The model calculated TLS management costs (presented in Table 66) by multiplying the likelihood of requiring prophylaxis or hospitalisation by the associated unit cost.

Table 66 TLS management costs

First-line treatment	% Patients who are at high risk for TLS	One-off cost, TLS prophylaxis management (£)	% Patients who experience TLS hospitalisation	One-off cost, hospitalisation for treatment-emergent TLS (£)
FCR-suitable population				
I+V	0%		0%	
FCR	0%		0%	
FCR-unsuitable and high-risk population				
I+V	42.5%	3,796.00[†ǂ]	0%	1,586.01
O-Clb	0%		5.7%	
VenO	65.1%		13.4%	
Acalabrutinib	0%		0%	
Ibrutinib monotherapy	0%		0%	

FCR = fludarabine, cyclophosphamide, rituximab; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; TLS = tumour lysis syndrome; VenO = venetoclax + obinutuzumab

† One-off cost is derived from the product of frequency of resources involved in prophylaxis (Anti-hyperuricemics = 15, Blood chemistry monitoring = 9, Outpatient visits = 3, Hospitalisation = 2) and their corresponding unit costs (Anti-hyperuricemics = £1.61, Blood chemistry monitoring = £9.59, outpatient visits = £171.18, and hospitalisation = £1,586.01)

ǂ The frequency of resources involved in prophylaxis were derived from the venetoclax SmPC (8)

B.3.5.4 Disease management cost

Calculation of disease management expenses involved application of a micro-costing approach that itemised and quantified healthcare resource utilisation, identified and multiplied suitable unit costs for each resource type and then summed across resources to arrive at the estimate used in the model.

Resource utilisation was assumed to vary for patients in the PF and PD (includes PF 2L and PPS) states and was sourced from UK expert clinical opinion.(110) Unit costs were based on the National Schedule of NHS costs (Year 2019-20).(111) Resource utilisation, unit costs and estimated per-cycle disease management costs for the PF and PD states are reported in Table 67 and Table 68, respectively. Resource utilisation is assumed to be equivalent across all comparators and populations aligned with other NICE TAs in first-line CLL.(1, 2)

Table 67 PF health state costs and resource use

Resource	Frequency per Month	Unit cost (£)	Cost per Month (£)
Full blood count	0.42	2.56	1.08
Chest X ray	0.08	33.61	2.69
BM exam	0.00	593.97	0.00
LDH	0.17	1.20	0.20
Haematologist visits	0.33	171.18	56.49
CT scan	0.02	120.55	2.41
Renal – Urea and electrolytes test	0.33	6.00	1.98
Liver function test	0.33	8.39	2.77
Immunoglobin blood test	0.08	1.20	0.10
Inpatient non-surgical medical visit	0.08	560.31	44.82
Full blood transfusion	0.00	322.93	1.08
Total cost per Month			***112.54***
Total cost per Cycle			***105.53***

BM = bone marrow; CT = computed tomography; LDH = lactate dehydrogenase

Table 68 PD health state costs and resource use

Resource	Frequency per Month	Unit cost (£)	Cost per Month (£)
Full blood count	0.58	2.56	1.49
Chest X ray	0.08	33.61	2.80
BM exam	0.08	593.97	49.50
LDH	0.25	1.20	0.30
Haematologist visits	0.42	171.18	71.32
CT scan	0.17	120.55	20.09
Renal – Urea and electrolytes test	0.58	6.00	3.50
Liver function test	0.58	8.39	4.90
Immunoglobin blood test	0.08	1.20	0.10
Inpatient non-surgical medical visit	0.17	560.31	93.39
Full blood transfusion	0.08	322.93	26.91
Total cost per month			***274.29***
Total cost per cycle			***252.33***

BM = bone marrow; CT = computed tomography; LDH = lactate dehydrogenase

B.3.5.5 Concomitant medication

Patients in the FCR arm of the FCR-suitable population receive additional concomitant treatment in the form of a growth factor. Details regarding the dosing regimen and unit

costs are presented in Table 69.(112) This is not applicable to the I+V arm of the FCR-suitable population, FCR-unsuitable or high-risk populations.

Table 69 Growth factor dosing and unit costs

Treatments	Dosing Regimen	Concentration	Vial size	Cost per piece (£)	Cost per mg (£)	Total cost (£)
Granulocyte colony-stimulating factor	0.01 mg/kg for 6 days in each chemotherapy cycle for a maximum of six cycles[†]	0.6mg/mL	0.5 mL	52.70	175.7	5,584.1[†]

[†] The recommended dose of Neupogen (G-CSF) is 1 MU (10 µg)/kg/day for 5-7 days (assumed to be 6 days) in a 28-day cycle. G-CSF is administered along with FCR whose dosing regimen lasts for a maximum of 6 cycles

[†] The total cost of G-CSF is applied as a one-off and is applicable only to patients receiving FCR at the start of the model cycle

B.3.5.6 Terminal care cost

The cost of end-of-life care is applied as a one-off cost for each incident death event in the model. Consistent with the approach applied in other NICE TAs,(2, 108, 113) this cost was derived from the value reported by Round, Jones and Morris 2015,(114) who estimated the direct and indirect cost for lung, breast, colorectal and prostate patients at the end of life in England and Wales. This value was then inflated to 2020 GBP (£7,569.34).

B.3.6 Severity

The severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS was calculated for all three populations of interest. The extent of unmet health need is reflected by the absolute and proportional QALY shortfall.

Inputs for the QALY shortfall calculation are informed by clinical trials and published data. The cohort characteristics in the E1912 trial are assumed to be representative of the FCR-suitable population, with a median age of 58 years and 67.3% being male. The

GLOW trial is representative of the FCR-unsuitable population, with a median age of 71 years and 57.8% of them being males.

Table 70 Summary features of QALY shortfall analysis

Parameter	Value	Source / Note
FCR-suitable population		
Mean starting age	58 years	Median age of E1912(83)
Proportion of male	67.3%	Male % in the E1912(83)
FCR-unsuitable population		
Mean starting age	71 years	Median age of the GLOW trial population; GLOW CSR, November 2021(70)
Proportion of male	57.8%	GLOW CSR, November 2021(70)

CSR = clinical study report; FCR = fludarabine, cyclophosphamide, rituximab

Health state utilities inputs were informed by the EQ-5D analysis based on the GLOW trial (Table 71). For calculation of QALYs for patients without the condition over the remaining life expectancy, UK life tables and UK age and sex adjusted utilities based on Hernandez Alava et al. 2022(99) have been used. The current standard of care for the FCR-suitable population is FCR. The current standard of care composition for the FCR-unsuitable population is [redacted] VenO, [redacted] acalabrutinib, and [redacted] O-Clb. For the current high-risk population, the standard of care treatment composition is [redacted] VenO, [redacted] acalabrutinib, and [redacted] ibrutinib respectively.

Table 71 Summary of health state benefits and utility values for QALY shortfall analysis

State	Progression-free	Progressed
Health state utilities - FCR-suitable	[redacted]	[redacted]
Health state utilities – FCR-unsuitable	[redacted]	[redacted]
Health state utilities – high-risk	[redacted]	[redacted]

FCR = fludarabine, cyclophosphamide, rituximab

The results of the QALY shortfall analysis show that the technology does not meet the criteria for a severity weight in the three populations according to proportional shortfall (at least 85%).

Table 72 Summary of QALY shortfall analysis

Population	Remaining QALYs without disease	Remaining QALYs with disease	Absolute shortfall	Proportional shortfall	QALY weight
FCR-suitable patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FCR-unsuitable patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High-risk patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FCR = fludarabine, cyclophosphamide, rituximab; QALY = quality-adjusted life year

B.3.7 Uncertainty

There are no specific uncertainties beyond those inherent to any evaluation of a complex haematology product.

B.3.8 Summary of base case analysis inputs and assumptions

B.3.8.1 Model inputs

FCR-suitable population

The tables below present the inputs for the base case analyses in the FCR-suitable population (Table 73).

FCR-unsuitable population

The tables below present the inputs for the base case analyses in the FCR-unsuitable population (Table 74).

High-risk population

The tables below present the inputs for the base case analyses in the high-risk population (Table 75).

Table 73 Summary of base case analysis inputs for the FCR-suitable population

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Starting age	58	NA	Table 20
% male	67.3%	NA	Table 70
Time horizon	40 years	NA	Table 20
Discount—health	3.5%	NA	NICE reference case
Discount—cost	3.5%	NA	NICE reference case
Cycle length	28 days	NA	Table 20
SMR	1.00	NA	Assumption
BSA	2.1 m^2	SE = 0.21 (Normal)	Table 56
Weight	88.3 kg	SE = 9.01 (Normal)	
Efficacy settings			
PFS 1L: I+V; HR vs. FCR	[redacted] (ATC vs. E1912 FCR)	SE = [redacted] (Weibull)	PF 1L to PF 2L or PPS
PFS 1L: FCR	Weibull (E1912)	Multivariate Normal	
AMR death in PFS 1L: I+V	[redacted] (CAPTIVATE)	SE = [redacted] (Normal)	PF 1L to Death
AMR death in PFS 1L: FCR	[redacted] (E1912)	SE = [redacted] (Normal)	
PFS 2L: All comparators	Exponential	Multivariate Normal	PF 2L to PPS
AMR death in PFS 2L: All comparators	[redacted]	SE = [redacted] (Normal)	PF 2L to Death
AMR death in PPS: All comparators	[redacted]	SE = [redacted] (Normal)	PPS to Death
Acquisition cost per cycle[†]			
I+V: Ibrutinib	[redacted] for 15 cycles	±20% (Gamma)	B.3.5.1 Drug acquisition costs
I+V: Venetoclax	£1,031 (C4); £4,459 (C5 to C15)	±20% (Gamma)	
FCR: Fludarabine	£424 (C1 to C6)	±20% (Gamma)	
FCR: Cyclophosphamide	£80 (C1 to C6)	±20% (Gamma)	
FCR: Rituximab	£1,318 (C1); £1,647 (C2 to C6)	±20% (Gamma)	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Drug administration cost per cycle			
FCR: Fludarabine	£664 (C1 to C6)	±20% (Gamma)	B.3.5.1 Drug administration costs
FCR: Cyclophosphamide	£664 (C1 to C6)	±20% (Gamma)	
FCR: Rituximab	£221 (C1 to C6)	±20% (Gamma)	
Subsequent treatment cost per cycle[†]			
Ibrutinib monotherapy	[redacted] (C1 to progression)	±20% (Gamma)	B.3.5.1 Subsequent treatment cost
Acalabrutinib monotherapy	£4,684 (C1 to progression)	±20% (Gamma)	
VenR: Venetoclax	£58 (C1); £2,178 (C2); £4,646 (C3 to C28)	±20% (Gamma)	
VenR: Rituximab	£2,829 (C3); £1,572 (C4 to C6)	±20% (Gamma)	
Subsequent treatment administration cost per cycle			
VenR: Rituximab	£443 (C3); £221 (C4 to C6)	±20% Gamma	B.3.5.1 Subsequent treatment cost
Disease management			
Routine care in PF 1L	£106	SE = 10.8 (Gamma)	B.3.5.4 Disease management cost
Routine care in PD	£252	SE = 25.7 (Gamma)	
One-off G-CSF cost (applicable only to FCR)	£5,584	SE = 570 (Gamma)	Table 69
Terminal care	£7,569	SE: 772 (Gamma)	B.3.5.6 Terminal care cost
One-off AE cost			
I+V	£789	SE = 80.5 (Gamma)	B.3.5.2 AE management cost
FCR	£3,044	SE = 310.7 (Gamma)	
One-off AE disutility			
I+V	-0.003	SE = 0.0002 (Beta)	B.3.4.4 Adverse events
FCR	-0.013	SE = 0.0007 (Beta)	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utility*			
PF 1L	[redacted]	SE = [redacted] (Beta)	B.3.4 Measurement and valuation of health effects
PD	[redacted]	SE = [redacted] (Beta)	

1L = first line; 2L = second line; AE = adverse event; AMR = annualised mortality ratio; ATC = average treatment effect in the control population; BSA = body surface area; CI = confidence interval; FCR = fludarabine, cyclophosphamide, rituximab; G-CSF = granulocyte colony-stimulating factor; HR = hazard ratio; I+V = ibrutinib + venetoclax; NA = not applicable; PD = progressed disease; PF = progression free; PFS = progression-free survival; PPS = post-progression survival; SE = standard error; SMR = standardised mortality ratio; VenR = venetoclax + rituximab

† Ibrutinib acquisition costs are based on the confidential PAS. All other drug acquisition costs are based on list prices

*Utility values adjusted to reflect age of the FCR-suitable/E1912 population

Table 74 Summary of base case analysis inputs for the FCR-unsuitable population

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Starting age	71	NA	Table 20
% male	57.8%	NA	Table 70
Time horizon	30 years	NA	Table 20
Discount—health	3.5%	NA	NICE reference case
Discount—cost	3.5%	NA	NICE reference case
Cycle length	28 days	NA	Table 20
SMR	1.00	NA	Assumption
BSA	1.87 m^2	SE = 0.19 (Normal)	Table 56
Weight	77 kg	SE = 7.86 (Normal)	
Efficacy settings			
PFS 1L: I+V	KM + exponential (GLOW)	Multivariate Normal	PF 1L to PF 2L or PPS
PFS 1L: O-Clb	7-knot spline model	Multivariate Normal	
PFS 1L: VenO (HR vs. I+V)	[redacted]	SE = [redacted] (Normal)	
PFS 1L: Acalabrutinib (HR vs. I+V)	[redacted]	SE = [redacted] (Normal)	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AMR: Death in PFS 1L: I+V	[redacted] (GLOW)	SE = [redacted] (Normal)	PF 1L to Death
AMR: Death in PFS 1L: O-Clb	[redacted] (GLOW)	SE = [redacted] (Normal)	
AMR: Death in PFS 1L: VenO	[redacted] (Assumed to be the same as O-Clb from GLOW)	SE = [redacted] (Normal)	
AMR: Death in PFS 1L: Acalabrutinib	[redacted] (Assumed to be the same as O-Clb from GLOW)	SE = [redacted] (Normal)	
Acquisition cost per cycle[†]			
I+V: Ibrutinib	C1 to C15: [redacted]	±20% (Gamma)	B.3.5.1 Drug acquisition costs
I+V: Venetoclax	C4: £995.69 C5 to C15: £4,305.71	±20% (Gamma)	
O-Clb: Obinutuzumab	C1: £9,399.46 C2 to C6: £3,133.15	±20% (Gamma)	
O-Clb: Chlorambucil	C1 to C6: £40.72	±20% (Gamma)	
VenO: Venetoclax	C1: £59.97 C2: £2,245.05 C3 to C15: £4,789.44	±20% (Gamma)	
VenO: Obinutuzumab	C1: £9,936.00 C2 to C6: £3,312.00	±20% (Gamma)	
Acalabrutinib	C1 to progression: £4,683.96	±20% (Gamma)	
Drug administration cost per cycle			
O-Clb: Obinutuzumab	£664 (C1); £221(C2 to C6)	Gamma	B.3.5.1 Drug administration costs
VenO: Obinutuzumab	£664 (C1); £221(C2 to C6)	Gamma	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Subsequent treatment cost per cycle[†]			
Ibrutinib monotherapy	[redacted] (C1 to progression)	±20% Gamma	B.3.5.1 Subsequent treatment cost
VenR: Venetoclax	£4,684 (C1 to progression)	±20% Gamma	
VenR: Rituximab	£58.1 (C1); £2,178 (C2); £4,646 (C3 to C28)	±20% Gamma	
Acalabrutinib monotherapy	£2,829 (C3); £1,572 (C4 to C6)	±20% Gamma	
Subsequent treatment administration cost per cycle			
VenR: Rituximab	£443 (C3); £221 (C4 to C6)	±20% Gamma	B.3.5.1 Subsequent treatment cost
Disease management			
Routine care in PF 1L	£106	SE = 10.8 (Gamma)	B.3.5.4 Disease management cost
Routine care in PD	£252	SE = 25.7 (Gamma)	
Terminal care	£7,569	SE: 772 (Gamma)	B.3.5.6 Terminal care cost
TLS management cost	£3,796	SE = 387 (Gamma)	B.3.5.3 TLS management cost
I+V TLS high risk	42.5%	SE = 0.043 (Gamma)	
VenO TLS high risk	65.1%	SE = 0.066 (Gamma)	
TLS hospitalisation cost	£1,586	SE = 162 (Gamma)	
O-Clb TLS hospitalisations	5.7%	SE = 0.06 (Gamma)	
VenO TLS hospitalisations	13.4%	SE = 0.014 (Gamma)	
One-off AE cost			
I+V	£1,547.26	SE = 158 (Gamma)	B.3.5.2 AE management cost
O-Clb	£1,638.70	SE = 167 (Gamma)	
VenO	£1,846.26	SE = 188 (Gamma)	
Acalabrutinib monotherapy	£514.09	SE = 52 (Gamma)	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
One-off AE disutility			
I+V	-0.007	SE = 0.0004 (Beta)	B.3.4.4 Adverse events
O-Clb	-0.006	SE = 0.0003 (Beta)	
VenO	-0.007	SE = 0.0004 (Beta)	
Acalabrutinib monotherapy	-0.002	SE = 0.0001 (Beta)	
Utility*			
PF 1L	[redacted]	SE = [redacted] (Beta)	B.3.4 Measurement and valuation of health effects
PD	[redacted]	SE = [redacted] (Beta)	

1L = first line; 2L = second line; AE = adverse event; AMR = annualised mortality ratio; BSA = body surface area; CI = confidence interval; HR = hazard ratio; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; NA = not applicable; O-Clb = obinutuzumab + chlorambucil; PD = progressed disease; PF = progression free; PFS = progression-free survival; SE = standard error; SMR = standardised mortality ratio; TLS = tumour lysis syndrome; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab
† Ibrutinib acquisition costs are based on the confidential PAS. All other drug acquisition costs are based on list prices
* Adjusted to reflect age of GLOW trial population

Table 75 Summary of base case analysis inputs for the high-risk population, where different from FCR-unsuitable population

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Efficacy settings			
PFS 1L: I+V	KM + exponential (GLOW)	Multivariate Normal	B.3.3.4 High-risk population
PFS 1L: VenO (HR vs. I+V)	[redacted]	SE = [redacted] (Normal)	

Variable	Model input (base case)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
PFS 1L: Acalabrutinib (HR vs. I+V)	[redacted]	SE = [redacted] (Normal)	
PFS 1L: Ibrutinib	Same as acalabrutinib		
Acquisition cost per cycle†			
Ibrutinib monotherapy	[redacted]	±20% (Gamma)	B.3.5.1 Drug acquisition costs
One-off AE cost			
Ibrutinib monotherapy	£806.36	82.3 (Gamma)	B.3.5.2 AE management cost
One-off AE disutility			
Ibrutinib monotherapy	-0.005	0.0002	B.3.4.4 Adverse events

1L = first line; AE = adverse event; CI = confidence interval; HR = hazard ratio; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; PFS = progression-free survival; VenO = venetoclax + obinutuzumab

† Ibrutinib acquisition costs are based on the confidential PAS. All other drug acquisition costs are based on list prices

B.3.8.2 Assumptions

A list of all assumptions in the model are provided with justification, particularly any assumptions that do not align with the reference case.

FCR-suitable population

The tables below present the key assumptions for the FCR-suitable population (Table 76).

FCR-unsuitable population

The tables below present the key assumptions for the FCR-unsuitable population (Table 77).

High-risk population

The tables below present the key assumptions for the high-risk population (Table 78).

Table 76 Summary of key model assumptions for the FCR-suitable population

Model Input	Assumption	Rationale
Time horizon	40	Capture a lifetime horizon per NICE guidance given starting median age of 58 years derived from E1912; Refer Table 20
FCR PFS	PFS from the E1912 trial assumed to be representative of an FCR-suitable population	More recent Phase 3 trial and provides long-term data (70m follow-up) and with access to IPD for earlier data cuts; Refer PF 1L to PF 2L or PPS
PFS 2L and PPS source	RESONATE Ibrutinib OS data (patients with 1-2 prior therapies only) used to inform PPS	Provides a proxy for the PFS of patients progressing after first-line therapy Used to model PFS 2L and PPS in NICE TA689 (2)
Treatment-free interval	Patients do not initiate subsequent treatment for 14 cycles upon progression in 1L	Due to the relapsing and remitting nature of CLL, patients experience a TFI between progression in 1L and starting 2L. 14 cycles was derived from the ERG preferred analysis in TA689(2) and an advisory board of clinical and health economic experts (4)
Proportion receiving subsequent treatment	Assume 100% of patients alive after progression will receive a subsequent treatment	Derived from clinical expert opinion; there is a negligible proportion of patients who do not receive subsequent treatment upon progression, who go on to receive BSC
Distribution of subsequent treatment	After FD I+V, patients may receive BTKi in subsequent line	Derived from expert clinical expert opinion (110)
Subsequent treatment efficacy	No difference is assumed in the efficacy of subsequent treatments	Was confirmed by the March 2022 advisory board of clinical and health economic experts (4)
Duration of subsequent treatment	Assume that 2L PFS captures the duration that patients may receive currently approved drugs (ibrutinib, acalabrutinib or VenR [up to a maximum of 24 cycles])	Patients receive 2L treatment up until they experience progression or death. This approach was also considered to model subsequent treatment duration in prior NICE appraisal TA689 (2)
PFS 1L Utility Source	Assume that utility from GLOW for a mean age of 71 can be age adjusted to reflect an FCR-suitable younger population	HRQoL was not captured in CAPTIVATE; This approach was validated by an advisory board of clinical and health economic experts (4)

Model Input	Assumption	Rationale
PFS 1L Utility Values	Assume no difference in the health state utility values by treatment except impact of AE disutilities	No meaningful difference in health state utility seen across treatment arms. This was also the case in TA689(2)
Administration costs	Oral therapies were assumed not to incur an administration cost	Assumption was accepted in prior NICE TAs (TA663 and TA689);(1, 2) Oral therapies can be administered at home
Monitoring costs	Monitoring costs assumed equivalent across treatment arms	Assumption was accepted in prior NICE TAs(1, 2)

1L = first line; 2L = second line; AE = adverse event; BSC = best supportive care; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukaemia; ERG = evidence review group; FCR = fludarabine, cyclophosphamide, rituximab; FD = fixed duration; HRQoL = health-related quality of life; IPD = individual patient data; I+V = ibrutinib + venetoclax; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PPS = post-progression survival; TA= technology appraisal; TFI = treatment-free interval; VenR = venetoclax + rituximab

Table 77 Summary of key model assumptions for the FCR-unsuitable population, where different from FCR-suitable population

Model Input	Assumption	Rationale
Time horizon	30	Capture a lifetime horizon as per NICE guidance given the starting median age of 71 years; Refer Table 20
I+V PFS and death during PFS	Death during PFS in 1L uses the KM curve from the trial initially and then a mortality based on O-Clb	This enables the model to capture the early death events in the I+V arm which was deemed important by the March 2022 advisory board of clinical and health economic experts (4)
I+V extrapolation	Assumes the most conservative estimates for long-term PFS	Validated by the March 2022 advisory board of clinical and health economic experts (4); Projections using analysis confirmed by long-term PFS from the RESONATE-2 BTKi arm(6) and further validated by clinical expert opinion in May 2022.(5)
Comparative efficacy	Anchored analysis used to estimate relative difference of I+V vs. VenO and acalabrutinib	Validated by the March 2022 advisory board of clinical and health economic experts (4) Projections using analysis validated by clinical expert opinion in May 2022.(5)

Model Input	Assumption	Rationale
Other treatment death during 1L and 2L PFS	Death during PFS 1L is assumed the same for VenO, acalabrutinib and O-Clb; death during PFS during 2L is assumed to be the same for all treatments.	In treatment naïve patients, pre-progression mortality is expected to be low and consistent across treatments; Lack of IPD for external comparators
PFS 1L Utility Source	GLOW trial reflects the utility of patients in the progression-free health state	Newer trials have all consistently collected similar PF utility values(1, 2) Refer to B.3.4.1 Health-related quality-of-life data from clinical trials

1L = first line; 2L = second line; BTKi = Bruton's tyrosine kinase inhibitor; IPD = individual patient data; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; NICE = National Institute for Health and Care Excellence; O-Clb = obinutuzumab + chlorambucil; PF = progression-free; PFS = progression-free survival; VenO = venetoclax + obinutuzumab

Table 78 Summary of key model assumptions for the high-risk population, where different from FCR-unsuitable

Model Input	Assumption	Rationale
Time horizon	Same assumption as in FCR-unsuitable population (Table 77)	
Comparative efficacy	Anchored analysis used to estimate relative difference of I+V vs. VenO and acalabrutinib Ibrutinib monotherapy and acalabrutinib monotherapy assumed to have the same efficacy	Same assumptions as for the FCR-unsuitable population; this approach was validated by clinical expert opinion in May 2022 (5) Assumption of equivalent efficacy between ibrutinib and acalabrutinib accepted in TA689 (2)
Other treatment death during 1L and 2L PFS	Death during PFS is assumed the same for VenO, acalabrutinib and ibrutinib; death during PFS during 2L is assumed to be the same for all treatments.	Pre-progression mortality in treatment-naïve patients is expected to be low and consistent across treatments; Equivalence of subsequent treatment efficacy was validated by the March 2022 advisory board of clinical and health economic experts (4)

1L = first line; 2L = second line; FCR = fludarabine, cyclophosphamide, rituximab; I+V = ibrutinib + venetoclax; PFS = progression-free survival; TA = technology appraisal; VenO = venetoclax + obinutuzumab

B.3.9 Results

The following sections describe the deterministic results of the cost-effectiveness analyses conducted for the three populations of interest. This section also explores the uncertainty associated with the parameters used in calculating cost-effectiveness and reports the probabilistic sensitivity analyses (PSA) and the deterministic sensitivity analyses (DSA).

B.3.9.1 FCR-suitable population

Deterministic results

The table below presents the base case results for the FCR-suitable population.

Table 79 Deterministic Results: FCR-suitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
FCR	[redacted]	10.83	[redacted]	[redacted]	2.01	[redacted]	£8,277	[redacted]	[redacted]
I+V	[redacted]	12.84	[redacted]	-	-	-	-	-	-

FCR = fludarabine, cyclophosphamide, rituximab; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; WTP = willingness to pay

Probabilistic sensitivity analyses

PSA was conducted to assess the parametric uncertainty associated with the base case model results. All key parameters were assigned probability distributions from which random sampling was done over 1,000 simulations. Where uncertainty data were not available for an input, standard errors of 20% of the mean values were assumed. The base case PSA results for the FCR-suitable population are presented in Table 80. The average PSA results largely align with the deterministic results.

Table 80 Average results based on the PSA: FCR-suitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
FCR	[redacted]	10.84	[redacted]	[redacted]	2.05	[redacted]	£6,260	[redacted]
I+V	[redacted]	12.89	[redacted]	-	-	-	-	-

FCR = fludarabine, rituximab, cyclophosphamide; ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year

The cost-effectiveness planes and acceptability curves for the FCR-suitable population, comparing I+V to FCR, are presented in Figure 32 and Figure 33 respectively. The clouds of points in the scatterplot are relatively diffuse, suggesting some degree of uncertainty. There's a clear separation between I+V and FCR outcomes. I+V is almost always associated with higher QALYs compared to FCR but there's more uncertainty on the costs. The cost-effectiveness acceptability curves indicate that I+V is likely to be cost-effective at a willingness to pay (WTP) threshold of £30,000/QALY.

Figure 32 Cost-effectiveness plane: FCR-suitable population

FCR = fludarabine, rituximab, cyclophosphamide; I+V = ibrutinib + venetoclax; QALY = quality-adjusted life year

Figure 33 Cost-effectiveness acceptability curve: FCR-suitable population

FCR = fludarabine, rituximab, cyclophosphamide; WTP = willingness to pay

Deterministic sensitivity analyses

DSAs were conducted by varying model parameters between the upper and lower 95% CIs of the base case values. Inputs for which 95% CIs were not available were varied by +20%. Appendix S shows the parameters included in the DSA and their corresponding lower and upper values for the FCR-suitable population. Figure 34 shows the DSA around the incremental net monetary benefit of FCR vs. I+V for a WTP threshold of £ 30,000. The model was highly sensitive to the comparative efficacy of I+V vs. FCR and the FCR extrapolation parameters (Weibull distribution) and the drug acquisition cost of I+V.

Figure 34 DSA results of INMB per QALY of FCR vs. I+V

1L = first line; 2L = second-line; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; FCR = fludarabine, rituximab, cyclophosphamide; G-CSF = granulocyte colony-stimulating factor; HR = hazard ratio; PF = progression-free; PFS = progression-free survival; PPS = post-progression survival; VenR = venetoclax + rituximab

B.3.9.2 FCR-unsuitable population

Deterministic results

The tables below present the results for the base case analyses in the FCR-unsuitable population (Table 81). The total costs were highest for acalabrutinib monotherapy, relatively similar for O-Clb and VenO and lowest for I+V. The total QALYs were highest for acalabrutinib, followed by I+V, VenO and O-Clb.

I+V is less costly (incremental cost of [redacted]) and slightly less effective (incremental QALY of [redacted]) than acalabrutinib, resulting in a highly cost-effective ICER of [redacted] (southwest quadrant ICER). At a WTP threshold of £30,000/QALY, the incremental net monetary benefit was estimated to be [redacted]. I+V is seen as highly cost-effective, as the cost savings [redacted] are proportionately greater than the marginal reduction [redacted] in QALYs.

Table 81 Deterministic Results: FCR-unsuitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.88	[redacted]	-	-	-	-		
VenO	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]
O-Clb	[redacted]	8.14	[redacted]	[redacted]	1.74	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,546,602)†	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay
† Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted for the FCR-unsuitable population following the same methodology as for the FCR-suitable population (B.3.9.1 Probabilistic sensitivity analyses). The base case PSA results for the FCR-suitable population are presented in Table 82. The results of the deterministic analyses and PSA were consistent.

Table 82 Average results based on the PSA: FCR-unsuitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	9.88	[redacted]	-	-	-	-	-
VenO	[redacted]	9.51	[redacted]	[redacted]	0.37	[redacted]	Dominant	[redacted]
O-Clb	[redacted]	8.21	[redacted]	[redacted]	1.67	[redacted]	Dominant	[redacted]
Acalabrutinib	[redacted]	10.29	[redacted]	[redacted]	-0.41	[redacted]	less costly, less effective (£1,653,738) †	[redacted]

ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab
†Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

The cost-effectiveness planes and acceptability curves for the FCR-unsuitable population, comparing I+V to O-Clb, VenO and acalabrutinib are presented in Figure 35 and Figure 36, respectively. The clouds of points in the scatterplot are relatively diffuse, suggesting some degree of uncertainty. I+V is always associated with more benefits and lower costs when compared to O-Clb indicating a dominant relationship. Acalabrutinib is always more costly than other treatments in the analysis. There is greater uncertainty on VenO outcomes due to the wide CI of the PFS HR [redacted]. The cost-effectiveness acceptability curves indicate that I+V is the most cost-effective treatment at a WTP threshold of £30,000.

Figure 35 Cost-effectiveness plane: FCR-unsuitable population

I+V = ibrutinib + venetoclax; QALY = quality-adjusted life year; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab

Figure 36 Cost-effectiveness acceptability curve: FCR-unsuitable population

WTP = willingness to pay

Deterministic sensitivity analyses

Appendix S shows the parameters included in the DSA and their corresponding lower and upper values for the FCR-suitable population.

Figure 37, Figure 38 and Figure 39 show the DSA around the incremental net monetary benefit of O-Clb, VenO, and acalabrutinib vs. I+V for a WTP threshold of £30,000. DSA for the ICER/QALY parameter was not presented as the model resulted in dominant ICERs for I+V for some parameters as well as ICERs falling into the southwest quadrant.

Figure 37 DSA results of INMB per QALY of O-Clb vs. I+V

AE = adverse event; AMR = annualised mortality rate; DSA = deterministic sensitivity analysis; I+V = ibrutinib + venetoclax; INMB = incremental net monetary benefit; IV = intravenous; O-Clb = obinutuzumab + chlorambucil; I+V = ibrutinib plus venetoclax; FCR = fludarabine + cyclophosphamide + rituximab; QALY = quality-adjusted life year; PF 2L = progression-free second-line; PPS = post-progression survival; PF 1L = progression-free first-line; PPS = post-progression survival; VenR= venetoclax + rituximab

Figure 38 DSA results of INMB per QALY of VenO vs. I+V

AE = adverse event; AMR = annualised mortality rate; DSA = deterministic sensitivity analysis; I+V = ibrutinib + venetoclax; INMB = incremental net monetary benefit; IV = intravenous; I+V = ibrutinib plus venetoclax; QALY = quality-adjusted life year; PF 2L = progression-free second-line; PPS = post-progression survival; PF 1L = progression-free first-line; PPS = post-progression survival; VenO= venetoclax + obinutuzumab; TLS = tumour lysis syndrome

Figure 39 DSA results of INMB per QALY of acalabrutinib vs. I+V

AE = adverse event; AMR = annualised mortality rate; DSA = deterministic sensitivity analysis; I+V = ibrutinib + venetoclax; INMB = incremental net monetary benefit; IV = intravenous; I+V = ibrutinib plus venetoclax; QALY = quality-adjusted life year; PF 2L = progression-free second-line; PPS = post-progression survival; PF 1L = progression-free first-line; PPS = post-progression survival; TLS = tumour lysis syndrome

Based on the tornado diagrams, the INMB of O-Clb vs. I+V shows less variation when compared to the INMB of other comparators (VenO and acalabrutinib). The INMB VenO and acalabrutinib are highly sensitive to the comparative efficacy parameter (PFS HR vs. I+V). INMB of acalabrutinib was highly sensitive to the drug acquisition cost per cycle of acalabrutinib monotherapy and I+V whereas the INMB of VenO was sensitive to the drug acquisition cost of I+V. The variation of other parameters did not impact the model results to any considerable extent.

B.3.9.3 High-risk population

Deterministic results

The tables below present the results for the base case analyses in the high-risk population (Table 83).

Table 83 Deterministic Results: High-risk population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.88	[redacted]	-	-	-	-		
VenO	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]
Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£675,793)†	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,546,602)†	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay ; †Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted for the high-risk population following the same methodology as for the FCR-suitable population (B.3.9.1 Probabilistic sensitivity analyses). The base case PSA results for the high-risk population are presented in Table 84.

Table 84 Average results based on the PSA: High-risk population

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	9.88	[redacted]	-	-	-	-	-
VenO	[redacted]	9.54	[redacted]	[redacted]	0.34	[redacted]	Dominant	[redacted]
Ibrutinib	[redacted]	10.30	[redacted]	[redacted]	-0.42	[redacted]	less costly, less effective (£779,771)†	[redacted]
Acalabrutinib	[redacted]	10.28	[redacted]	[redacted]	-0.40	[redacted]	less costly, less effective (£1,891,990)†	[redacted]

ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + Obinutuzumab; †Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

The cost-effectiveness planes and acceptability curves for the high-risk population, comparing I+V to VenO, acalabrutinib, and ibrutinib are presented in Figure 40 and Figure 41 respectively. The values for I+V, acalabrutinib, and VenO in the cost-effectiveness plane is equivalent as that of the FCR-unsuitable population due to equivalence in inputs. Even though ibrutinib and acalabrutinib are assumed to have equivalent efficacy, ibrutinib incurs less cost and is separate from the acalabrutinib scatter. The cost-effectiveness acceptability curves indicate that I+V is the most cost-effective treatment at a WTP threshold of £30,000 and remains cost-effective until a threshold of £50,000.

Figure 40 Cost-effectiveness plane: High-risk population

I+V = ibrutinib + venetoclax; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab

Figure 41 Cost-effectiveness acceptability curve: High-risk population

WTP = willingness to pay

Deterministic sensitivity analyses

Appendix S shows the parameters included in the DSA and their corresponding lower and upper values for the high-risk population. Since the high-risk population assumes the same efficacy as that of the FCR-unsuitable populations, the DSA tornado diagrams remain consistent between the two populations for the common comparators (I+V, VenO, and acalabrutinib). Figure 38 and Figure 39 display the DSA for the INMB per QALY of VenO and acalabrutinib vs. I+V in the high-risk population.

Figure 42 displays the INMB per QALY for ibrutinib vs. I+V in the high-risk population.

The INMB of ibrutinib is highly sensitive to the drug acquisition cost per cycle of ibrutinib monotherapy and the comparative efficacy parameter (PFS HR vs. I+V).

Figure 42 DSA results of INMB per QALY of ibrutinib vs. I+V

AE = adverse event; AMR = annualised mortality rate; BSA = body surface area; DSA = deterministic sensitivity analysis; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; QALY = quality-adjusted life year; PF 1L = progression-free survival first-line; PF 2L = progression-free survival second-line; PPS = post-progression survival; VenR = venetoclax plus rituximab; AMR = annual mortality rate; AE = adverse event; IV = intravenous; TLS = tumour lysis syndrome

B.3.10 Scenario analysis

A list of scenarios ran in the cost-effectiveness model and their corresponding justification is provided in Table 85.

Table 85 List of scenario analysis conducted

Parameter	Base case	Scenario	Rationale
All populations			
Discount rate for costs	3.5%	1.5%	Explore the effect of discount rates
Discount rate for health	3.5%	1.5%	
% patients receiving 2L treatment	100%	80%	Not all patients receive 2L upon progression. Patients who are not eligible for 2L treatment go on to receive BSC
TFI	14 cycles	0 cycles	Patients receive 2L treatment immediately after progression as 2L inputs derived from RESONATE considers patients who start treatment immediately
Wastage	IV wastage considered; oral wastage not considered	IV and oral wastage considered	Explore the costs associated with oral wastage
Age adjustment	Considered	No age adjustment	Explore the effect of applying age adjustment to utilities
SMR	1.0	1.1, 1.15, 1.19	Explore the effect of patients experiencing an elevated mortality due to CLL
FCR-suitable population			
Time horizon	40 years	30 years	Explore effect of varying time horizons
		35 years	
I+V HR vs. FCR	ATC ([redacted])	ATO ([redacted]) ATT ([redacted])	Explore the effect of comparative efficacy vs. FCR
FCR extrapolation	Weibull	Gompertz, Gamma	Explore the uncertainty associated with FCR extrapolations

Parameter	Base case	Scenario	Rationale
FCR-unsuitable /High-risk population			
Time horizon	30 years	25 years 20 years	Explore the effect of shorter time horizons
VenO HR vs. I+V	Single HR - Adjusted for age, ECOG, CIRS, and TP53 mutation ([redacted])	HR within 12m: [redacted] HR after 12m: [redacted]	Explore the effect of time varying MAIC analysis
Acalabrutinib HR vs. I+V	Single HR - Adjusted for age, ECOG, CIRS, and TP53 mutation ([redacted])	HR within 12m: [redacted] HR after 12m: [redacted]	

2L = second line; ATO = average treatment effect in the combined/overall population; ATT = average treatment effect in the treated population; BSC = best supportive care; CIRS = Cumulative Illness Rating Scale; ECOG = Eastern Cooperative Oncology Group; FCR = fludarabine + cyclophosphamide + rituximab; HR = hazard ratio; IV = intravenous; I+V = ibrutinib + venetoclax; MAIC = matching-adjusted indirect comparison; SMR = standardised mortality ratio; TFI = treatment-free interval; VenO = venetoclax + obinutuzumab

Table 86 Scenario analysis: FCR-suitable population

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
Time horizon	30 years	I+V	[redacted]	12.64	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.74	[redacted]	[redacted]	[redacted]	£8,037
	35 years	I+V	[redacted]	12.80	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.81	[redacted]	[redacted]	[redacted]	£8,171
Discount rate for costs	1.5%	I+V	[redacted]	12.84	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£6,592
Discount rate for health	1.5%	I+V	[redacted]	15.45	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	12.65	[redacted]	[redacted]	[redacted]	£6,242
% patients receiving 2L treatment	80%	I+V	[redacted]	12.26	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.01	[redacted]	[redacted]	[redacted]	£12,023
TFI	0 cycle	I+V	[redacted]	12.84	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£4,211

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
I+V HR vs. FCR	ATO ([redacted])	I+V	[redacted]	12.67	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£11,500
	ATT ([redacted])	I+V	[redacted]	12.32	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£20,280
FCR extrapolation	Gompertz	I+V	[redacted]	12.18	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.55	[redacted]	[redacted]	[redacted]	£23,678
	Gamma	I+V	[redacted]	12.68	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.75	[redacted]	[redacted]	[redacted]	£11,824
IV wastage	Exclude	I+V	[redacted]	12.84	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£8,462
Oral wastage	Include	I+V	[redacted]	12.84	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£9,312
Utility age adjustment	Exclude	I+V	[redacted]	12.84	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	£7,752
SMR	1.1	I+V	[redacted]	12.76	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.80	[redacted]	[redacted]	[redacted]	£7,681
	1.15	I+V	[redacted]	12.72	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.78	[redacted]	[redacted]	[redacted]	£7,376
	1.19	I+V	[redacted]	12.69	[redacted]	[redacted]	[redacted]	-
		FCR	[redacted]	10.77	[redacted]	[redacted]	[redacted]	£7,134

2L = second line; ATO = average treatment effect in the combined/overall population; ATT = average treatment effect in the treated population; FCR = fludarabine + cyclophosphamide + rituximab; HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; IV = intravenous; LY = life year; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TFI = treatment-free interval

Table 87 Scenario analysis: FCR-unsuitable population

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
Time horizon	25 years	I+V	[redacted]	9.84	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.12	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.46	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.27	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,539,310)†
	20 years	I+V	[redacted]	9.56	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	7.99	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.24	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.99	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,484,565)†
Discount rate for costs	1.5%	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,811,314)†
Discount rate for health	1.5%	I+V	[redacted]	11.37	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	9.12	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	10.80	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	11.86	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,397,305)†
% patients receiving 2L treatment	80%	I+V	[redacted]	9.63	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	7.22	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	8.89	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.01	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,769,270)†
TFI	0 cycles	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,527,986)†
VenO HR vs. I+V	HR within 12M: [redacted]; HR after 12M: [redacted]	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	8.70	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)†
Acalabrutinib HR vs. I+V	HR within 12M: [redacted]; HR after 12M: [redacted]	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.95	[redacted]	[redacted]	[redacted]	Dominant
IV wastage	Exclude	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,054)†
Oral wastage	Include	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,547,982)†
Utility age adjustment	Exclude	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.14	[redacted]	[redacted]	[redacted]	Dominant

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,502,097)†
SMR	1.1	I+V	[redacted]	9.67	[redacted]	[redacted]	[redacted]	-
		O-Clb		8.07				Dominant
		VenO	[redacted]	9.33	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib		10.09				less costly, less effective (£1,584,991)†
	1.15	I+V	[redacted]	9.57	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.04	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.26	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.99	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,604,877)†
	1.19	I+V	[redacted]	9.50	[redacted]	[redacted]	[redacted]	-
		O-Clb	[redacted]	8.01	[redacted]	[redacted]	[redacted]	Dominant
		VenO	[redacted]	9.20	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.90	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,618,337)†

2L = second line; HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; IV = intravenous; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TFI = treatment-free interval; VenO = venetoclax + Obinutuzumab; †Represents ICER per QALY forgone for treatments in the less-costly less-effective (SW) quadrant

Table 88 Scenario analysis: High-risk population

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
Time horizon	25 years	I+V	[redacted]	9.84	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.46	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.27	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,539,310)†
		Ibrutinib	[redacted]	10.27	[redacted]	[redacted]	[redacted]	less costly, less effective (£672,441)†
	20 years	I+V	[redacted]	9.56	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.24	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.99	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,484,565)†
		Ibrutinib	[redacted]	9.99	[redacted]	[redacted]	[redacted]	less costly, less effective (£644,162)†
Discount rate for costs	1.5%	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,811,314)†
		Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£809,668)†
Discount rate for health	1.5%	I+V	[redacted]	11.37	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	10.80	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	11.86	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,397,305)†
		Ibrutinib	[redacted]	11.86	[redacted]	[redacted]	[redacted]	less costly, less effective (£610,092)†
	80%	I+V	[redacted]	9.63	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	8.89	[redacted]	[redacted]	[redacted]	Dominant

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
% patients receiving 2L treatment		Acalabrutinib	[redacted]	10.01	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,769,270)†
		Ibrutinib	[redacted]	10.01	[redacted]	[redacted]	[redacted]	less costly, less effective (£784,014)†
TFI	0 cycle	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,527,986)†
		Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£658,293)†
VenO HR vs. I+V	HR within 12M: [redacted]; HR after 12M: [redacted]	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO		8.70				Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)†
		Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£675,793)†
Acalabrutinib HR vs. I+V	HR within 12M: [redacted]; HR after 12M: [redacted]	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO		9.49				Dominant
		Acalabrutinib	[redacted]	9.95	[redacted]	[redacted]	[redacted]	Dominant
		Ibrutinib	[redacted]	9.95	[redacted]	[redacted]	[redacted]	Dominant
IV Wastage	Exclude	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,054)†

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
		Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£675,241)†
Oral Wastage	Include	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,547,982)†
		Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£723,273)†
Utility age adjustment	Exclude	I+V	[redacted]	9.88	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.49	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,502,097)†
		Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	[redacted]	less costly, less effective (£656,198)†
SMR	1.1	I+V	[redacted]	9.67	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.33	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	10.09	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,584,991)†
		Ibrutinib	[redacted]	10.09	[redacted]	[redacted]	[redacted]	less costly, less effective (£694,882)†
	1.15	I+V	[redacted]	9.57	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.26	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.99	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,604,877)†
		Ibrutinib	[redacted]	9.99	[redacted]	[redacted]	[redacted]	less costly, less effective (£704,649)†

Parameter	Scenario	Technology	Discounted costs	Discounted LYs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
	1.19	I+V	[redacted]	9.50	[redacted]	[redacted]	[redacted]	-
		VenO	[redacted]	9.20	[redacted]	[redacted]	[redacted]	Dominant
		Acalabrutinib	[redacted]	9.90	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,618,337)†
		Ibrutinib	[redacted]	9.90	[redacted]	[redacted]	[redacted]	less costly, less effective (£711,237)†

2L = second line; HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; IV = intravenous; LY = life year; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TFI = treatment-free interval; VenO = venetoclax + Obinutuzumab; †Represents ICER per QALY forgone for treatments in the less-costly less-effective (SW) quadrant

B.3.11 Subgroup analysis

In line with the scope, we considered three subgroups of patients: FCR-suitable patients, FCR-unsuitable patients and high-risk patients. However, since we consider these populations of co-equal importance, we have presented all three in our main section of results. No other subgroups were considered in the model.

B.3.12 Benefits not captured in the QALY calculation

The key benefit of I+V not captured by the QALY calculation is the regimen's potential to reduce medicalisation in all three populations compared to current standard of care. Medicalisation is the process whereby non-medical activities become subsumed into medical activities and so patients begin to define themselves by their disease rather than by a desire to lead a flourishing life. In CLL, this takes the form of patients having to plan life around frequent hospital visits and anticipate that their entire remaining lifespan will be spent on treatments with various side-effects. The risk of TLS associated with certain CLL treatments further compounds this burden, with more intensive measures (IV hydration, frequent monitoring, hospitalisation) being required as overall risk increases.(8, 59)

At a recent advisory board,(18) patients indicated that "they want to limit their number of hospital visits, as these can cause anxiety and disruption to their lives as well as being costly and difficult to organise," highlighting the significant impact medicalisation has on patients, which is missed by conventional health state assessment tools like the QALY. Since I+V is the first all-oral FD treatment for CLL, the frequency of hospital trips is reduced, and therefore the need for a patient to rely on transport from another person is reduced. The reduction in hospital visits also leads to less emotional stress and strain inflicted on patients who must take time off work or arrange for childcare, to accommodate hospital appointments. Furthermore, as demonstrated in the CAPTIVATE and GLOW studies, the 3-cycle lead in with ibrutinib reduced the risk of TLS and the proportion of patients with an indication for hospitalisation.(68, 70) Disutility for TLS prophylaxis was considered for inclusion in the model, but was ultimately not applied due to lack of data to inform this.

As I+V is a FD regimen, patients have both a shorter exposure to I+V than treat to progression comparators hence resulting in less time to experience AEs and a

(potentially) lengthy ‘treatment holiday’ between finishing first-line I+V and beginning the second-line treatment upon progression. While a ‘treatment holiday’ may not be important to all patients, for those patients for whom it is important it will not show up in QALY while in fact having a significant positive impact on their non-health QoL.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

Model structure

A review of existing NICE TAs in CLL was undertaken to determine the most appropriate modelling approach and model structure, healthcare resource use estimates and utility values (Table 20). Based on this review and the considerations described below, a semi-Markov cohort model was chosen as it captures clinically important aspects of the disease.

To select the model approach, the events of interest to capture were considered including progression (captured by PFS), post-progression including time on subsequent treatment. A cohort versus individual simulation approach was considered; however, there is little to no evidence available to support the heterogenous effect of patient characteristics on disease prognosis. Both Markov and survival partition cohort frameworks were also evaluated. A partitional survival model requires robust data to model long-term OS projections.(115) However, the I+V OS extrapolations using standard parametric functions of the CAPTIVATE and GLOW trials converge quickly with age and gender adjusted UK GPM (115) (within 3 years for CAPTIVATE and within 5 years for GLOW for all functions except exponential) creating rational inconsistencies (Figure 43 and Figure 44).

The semi-Markov framework prevents these inconsistencies by leveraging additional data more explicitly. The Markov framework allows for incorporation of relevant external data to inform clinical efficacy by line of therapy, thus explicitly capturing the costs and benefits associated with subsequent lines of treatment by considering different data sources for each treatment line. This is particularly useful given the immaturity of the OS data from the GLOW and CAPTIVATE trials. Additionally, incorporating subsequent lines of treatment in the model structure has high face

validity given the first-line treatment setting of the indications, as well as the potential remaining lifetime of the populations considered. A standard Markov model was also considered but was discarded in the favour of a semi-Markov approach as it enables the tracking of patients based on when they initiate second-line treatment.

A semi-Markov model approach has been used and accepted in the recent NICE appraisal of acalabrutinib in previously untreated CLL(TA689).(2) Finally, the model structure and approach was further confirmed during an advisory board of clinical (n=5) and health economic experts (n=3) conducted in March 2022.(4)

Figure 43 Extrapolation of I+V CAPTIVATE FD cohort OS, uncapped and capped by GPM hazards

FD = fixed duration; GPM = general population mortality; I+V = ibrutinib + venetoclax; OS = overall survival
Note: all extrapolations converge with the age adjusted UK GPM hazards within 3 years
The point at which the solid curves (standard parametric extrapolations) coincide with the dotted curves (standard parametric extrapolations capped by GPM) correspond to the timepoint at which the extrapolations converge with GPM.

Figure 44 Extrapolation of I+V GLOW OS

GPM = general population mortality; I+V = ibrutinib + venetoclax; OS = overall survival
Note: all extrapolations converge with the age adjusted UK GPM hazards in the first 3 years except for exponential which converges with GPM at 8 years
The point at which the solid curves (standard parametric extrapolations) coincide with the dotted curves (standard parametric extrapolations capped by GPM) correspond to the timepoint at which the extrapolations converge with GPM.

Long-term survival projections

The long-term survival projections obtained via direct projections of observed data and ITCs were selected based on the statistical fits and long-term clinical plausibility confirmed by an advisory board of clinical and health economic experts in March and based on clinical expert feedback sought in May 2022.(4, 5) (B.3.3.2 FCR-suitable , B.3.3.3 FCR-unsuitable population and B.3.3.4 High-risk population describe the selection and validation of clinical parameters in each population)

Since the model uses a semi-Markov approach, OS is calculated by summing the mortality in each health state, rather than directly projecting the OS survival data from the trials. The OS projections generated by the model were validated against the corresponding observed KM curves for each treatment. As stated earlier, the OS is derived from a combination of within trial and external data sources and the projections were not expected to be exactly in line with the KM curves; rather, OS KM data were useful as validation of the model projected survival.

Figure 45 shows the OS projections of technologies evaluated in the FCR-suitable population.

Figure 45 OS projections of technologies evaluated in the FCR-suitable population

FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; OS = overall survival

Figure 46 shows the OS projections of technologies evaluated in the FCR-unsuitable population, and the GPM. TA663 stated that clinicians assumed people treated with VenO in 1L setting will reach the GPM (at approximately 5 years) and will be assumed to be 'functionally cured'.(1)

Figure 46 OS projections of technologies evaluated in the FCR-unsuitable population

The OS projections of technologies evaluated in the high-risk population are the same as presented in Figure 46 for VenO and acalabrutinib. Since ibrutinib is assumed to have equivalent efficacy to acalabrutinib, the OS projection for ibrutinib is exactly the same as acalabrutinib.

Cost inputs

Unit costs of drug acquisition, administration, and resources used for routine follow-up were based on standard sources (latest version of BNF, eMIT and NHS reference costs). The types and frequencies of resources associated with routine follow-up, progression events, terminal care, breakdown of subsequent treatments were informed by UK clinical experts.(110)

B.3.13.2. Validation of Excel model

Upon completion of model programming, a rigorous and comprehensive quality check of the model was conducted to ensure the completed model contained no errors and worked as intended.

- A series of tests and checks were also conducted on the model engine. Among other reviews, the validator:
- Confirmed that all model inputs were correctly linked to the engine
- Checked all cells with “IF logic” in detail, confirming that the statements provided the correct value for each condition
- Traced all links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location
- Thoroughly reviewed and debugged all Visual Basic for Applications (VBA) code
- Searched for common Microsoft Excel® errors (e.g., !#REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors) and resolved them as needed
- Checked all text and formatting to ensure that there were no typographical errors or formatting irregularities

Finally, an extreme-value sensitivity analysis was conducted on all applicable model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the results included in this report.

B.3.14 Interpretation and conclusions of economic evidence

Summary of results

An evaluation of the cost-effectiveness of I+V against relevant comparators for the treatment of frontline CLL in the UK was conducted using a semi-Markov model. The analysis was conducted in line with the NICE reference case and the NICE final scope.

Results of the analysis demonstrate that I+V is cost-effective at the usual NICE threshold in all sub-populations vs. all comparators. In most cases, I+V dominates comparators (that is, is both less costly and more effective) and where I+V does not dominate the ICERs for comparators are well within the range usually considered cost-effective by NICE. These results were consistent across all scenario analyses run, and cost-effectiveness acceptability curves demonstrated that I+V had approximately a [redacted] chance of being the most cost-effective treatment at a WTP threshold of £30,000.

Key limitations of the economic analysis included immature data from CAPTIVATE and GLOW trials, lack of head-to-head data for some comparators and the paucity of available evidence in the high-risk population which led to the modelling assumption that the clinical efficacy of I+V in high-risk patients is equivalent to its efficacy in an FCR-unsuitable population. Ibrutinib which is a relevant comparator for the high-risk population was assumed to have equivalent efficacy to acalabrutinib. Scenario analyses were conducted to test the impact of these assumptions on the results, and long-term extrapolation estimates validated against external data where possible and clinical expert opinion.

Conclusion of economic evidence

CLL is generally an incurable disease, which can have a substantial negative impact on patients' QoL. CLL also imposes a considerable economic burden on patients, their families, the healthcare system and society.

Despite the advances made in CLL management over the last decade, patients with previously untreated CLL currently lack a convenient, all-oral, once daily, FD, chemotherapy-free treatment regimen that can be taken at home (without the need for infusion-based hospital treatments). As an all-oral FD regimen, I+V would address all these unmet needs.

The proposed positioning of I+V is in line with its full marketing authorisation, in patients with previously untreated CLL; FCR-suitable patients, FCR-unsuitable patients and high-risk patients.

The efficacy of I+V has been demonstrated in two trials; the multi-centre, open-label, phase II CAPTIVATE study, which found a deep and durable PFS response rate of [redacted] in FCR-suitable patients at 36 months (80% in the high-risk group) and the multi-centre, randomised, open-label, phase III GLOW study, which found a 79% reduction in the risk of progression or death vs. O-Clb in FCR-unsuitable patients with median 34.1 months follow-up. The safety profile of I+V combination is consistent with the known safety profiles of ibrutinib and venetoclax in other CLL regimens.

Results of the analysis demonstrated that I+V is cost-effective vs. FCR in the FCR-suitable population. In the FCR-unsuitable population, I+V is dominant vs. VenO and O-Clb and is less costly and less effective when compared to acalabrutinib. In the high-risk population, I+V is dominant vs. VenO and is less costly, less effective when compared to ibrutinib and acalabrutinib monotherapy. These results were consistent in all the scenario and sensitivity analyses conducted.

I+V offers benefits not captured in the QALY by its potential to reduce medicalisation in all three populations compared to current standard of care. In addition to the clinical benefits, I+V helps patients avoid a life of medicalisation by reducing hospital appointments and offering patients a 'treatment-free holiday' between finishing the FD treatment and beginning second line treatment upon progression. Furthermore,

the unique dual-oral posology of I+V has positive resource implications for the NHS, which is currently recovering from a global pandemic, by helping to alleviate the back-log of patients waiting to be treated.

The clinical evidence and economic analysis highlight that I+V would address significant unmet need and suggest that I+V should be reimbursed for the treatment of previously untreated CLL patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Summary of Information for Patients (SIP)

June 2022

File name	Version	Contains confidential information	Date
ID3860_Janssen_Ibrutinib_SIP_FINAL	FINAL	No	21st June 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Ibrutinib with venetoclax **Brand name**: Imbruvica® with Venclyxto®

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

This submission specifically deals with ibrutinib (Imbruvica®) in combination with venetoclax (Venclyxto®) to treat adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

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

Marketing authorisation (license) for ibrutinib in combination with venetoclax (I+V) is currently pending, and more details can be found in Section B.1.2 of the submission. Broadly, the marketing authorisation is anticipated to reflect the population of the submission, i.e., adult patients with previously untreated CLL. Janssen is currently in discussion with the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the wording and timelines of this indication and are unable to provide any details in this document.

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

The table below shows support from Janssen to relevant patient advocacy groups in the United Kingdom (UK), and how the company engages or supports these charities and/or patients who use

them. Financial support varies from annual support of core services to support of individual patients and/or staff to attend meetings or events.

Patient group:	Engagement/activity with each group:	Financial support provided:
Blood Cancer UK	Blood Cancer UK chaired and participated in the Janssen Haematology Summit in February 2021	£405
	Janssen gave a financial contribution to Blood Cancer UK for the Vaccines Taskforce	£130,000
Cancer 52	Janssen provided Cancer52 with funding towards their core activity in 2021	£9,000
Leukaemia Care	Janssen paid Leukaemia Care a fee for a representative of Leukaemia Care to contribute insights to a Janssen Campaign	£60
	Janssen paid Leukaemia Care a fee to input into a Janssen led HTA position paper	£210
	Janssen paid Leukaemia Care to support their core activities in 2021	£10,000
Lymphoma Action	Janssen have provided payment to Lymphoma Action to support their core activities in 2021	£8,000
Specialised Healthcare Alliance	Janssen provided the Specialised Healthcare Alliance funding, which was paid directly to an agency that provided secretariat support for the Alliance's work programme, focused on campaigning on overarching policies for people with rare conditions	£14,500
WMUK	Janssen have provided WMUK (Waldenstroms Macroglobulinemia UK) with funding to support their core activities in 2021	£7,500

Abbreviations: HTA = health technology assessment; UK = United Kingdom; WMUK = Waldenstroms Macroglobulinemia UK

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

What is chronic lymphocytic leukaemia (CLL)?

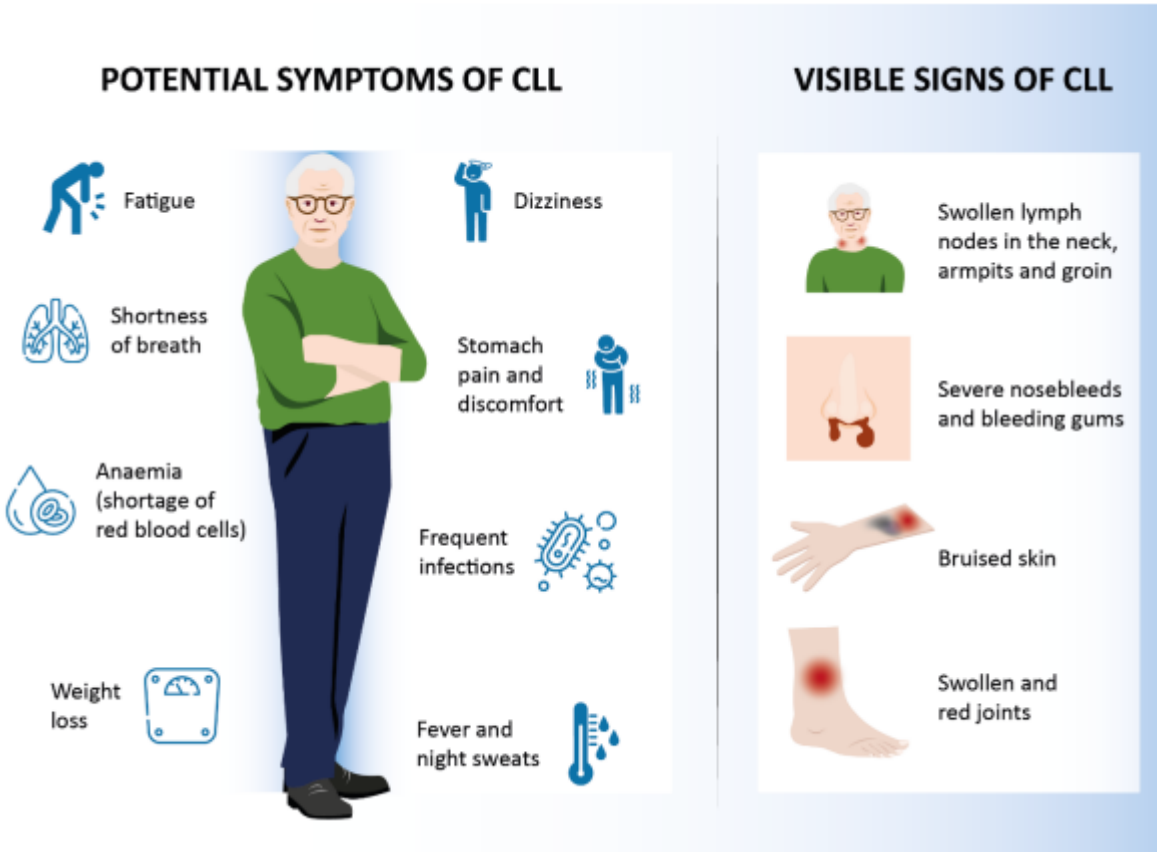
CLL is a type of blood cancer (leukaemia) which affects white blood cells called B cells. In healthy people, B cells play an important role in how the body fights off infections. B cells are made in the soft centre of bones (bone marrow). From there, they enter the blood and travel to other parts of the body where they can help to target infections, such as the spleen (organ which filters blood and helps guard against infection) and lymph nodes (small nodules which contain millions of infection-fighting cells).

In people with CLL, B cells have genetic changes, which stop them from fighting infections properly (they are 'abnormal'). The abnormal B cells build up in the bone marrow and blood, which stops normal blood cells from developing and working properly.(1) Because of their weaker immune system and low number of normal blood cells, people with CLL can experience a range of symptoms. They also often have a worse quality of life, and usually don't live as long as people without CLL.(2-4)

Signs and symptoms of CLL

People with CLL often do not show any signs or symptoms of their disease for months or years.(5) However, the most visible signs of CLL can include swollen lymph nodes in the neck, armpits and groin, abnormal bleeding such as severe nose bleeds and bleeding gums, bruised skin and swollen and red joints, as shown in **Figure 1**.(6, 7)

Figure 1: CLL signs and symptoms

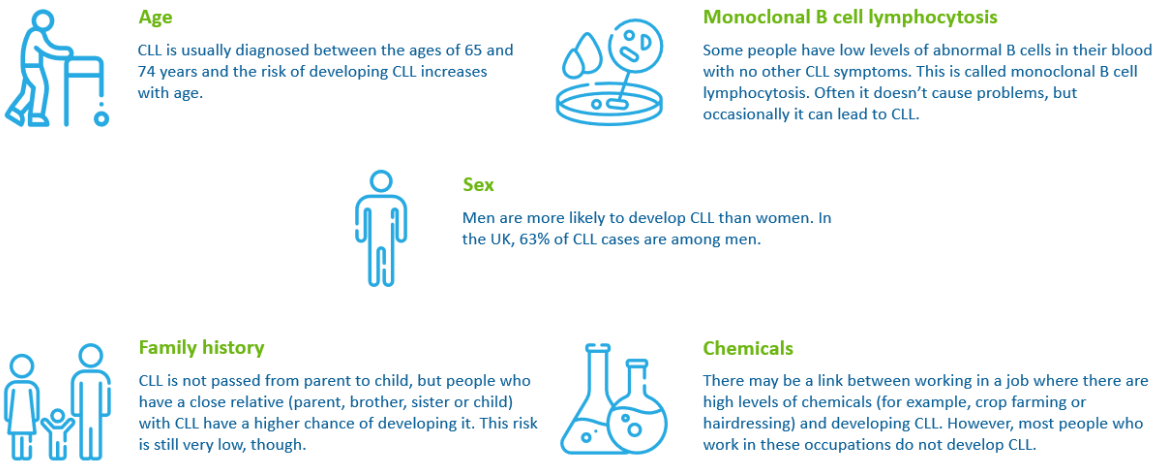


Abbreviations: CLL = chronic lymphocytic leukaemia

How many people have CLL?

In the UK, there are approximately 3,800 new CLL cases every year, making it the most common type of leukaemia among adults.(8) CLL can affect anyone, but there are some factors that can make a person more likely to develop CLL. These are called risk factors (**Figure 2**). (1, 9, 10)

Figure 2: Risk factors of CLL



Abbreviations: CLL = chronic lymphocytic leukaemia; UK = United Kingdom

Disease burden

People with CLL often require close monitoring and medical care to treat their condition and manage their symptoms. This can involve going to hospital to receive regular CLL treatment (for example, medicines that are given by a drip or injection into the bloodstream). It can also involve being given treatment for symptoms, such as antibiotics for frequent infections. In some cases, people with CLL might need to stay in hospital for extended periods of time, particularly if they have a severe infection. As many people with CLL are older, they often have other health conditions, such as heart or kidney problems. These conditions may also need treatment in hospital or regular prescriptions.(11, 12) It can be very time-consuming and expensive for patients to travel to and from appointments. It can also place a burden on families or carers who often accompany the person with CLL to their appointments.

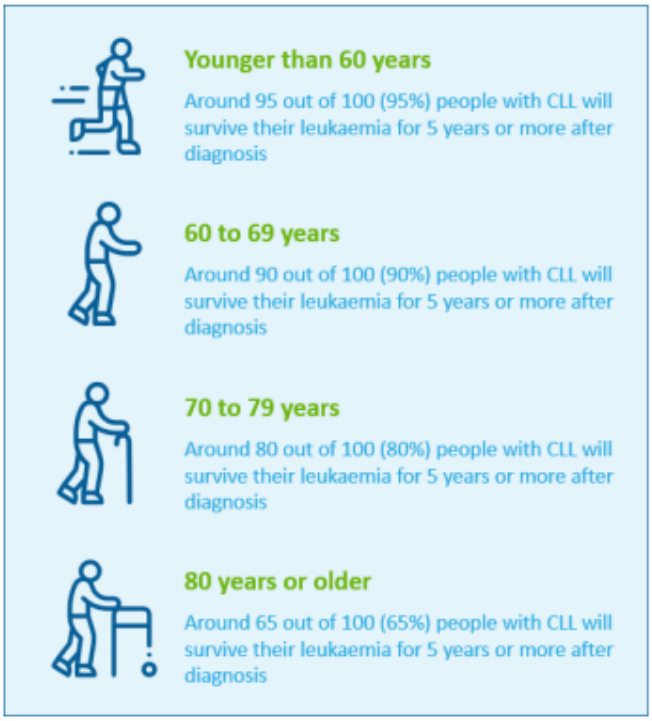
Because of their symptoms, treatment and time in hospital, people with CLL who are employed often need to take time off work. Some people might need to stop work altogether. This can mean that they lose some or all their income. This can be very stressful, and patients might need financial support from family or the government. On the other hand, many people with CLL are diagnosed in later life when they are already retired. For these individuals, their condition might mean that they can't support their family in other ways, such as providing childcare for grandchildren or carrying out household chores.

CLL can also be costly for the health system, employers and other people in society because of its impact on healthcare resources and work.

Life expectancy

CLL affects people in different ways. For some people, their condition will not have an impact on survival, but for others, their CLL will mean that they don't live as long as people without the condition.(3) The survival of people with CLL often depends on a person's age and how advanced their CLL was when they were diagnosed (**Figure 3**).(4, 13)

Figure 3: Survival of people with CLL in England by age



Abbreviation: CLL = chronic lymphocytic leukaemia

Emotional impact on patients

As there is no cure, being diagnosed with CLL can be difficult for patients. For example, many people with CLL worry about how the condition will affect their future health and ability to lead an active life.(14) In addition, when symptoms such as extreme tiredness, dizziness and stomach pain begin to show, it can become very difficult or uncomfortable for people with CLL to carry out everyday tasks and take care of themselves.(14) It can also be hard for them to socialise with friends or family because of their symptoms. This worsens the impact that the condition has on their quality of life.

Impact on families and carers of people with CLL

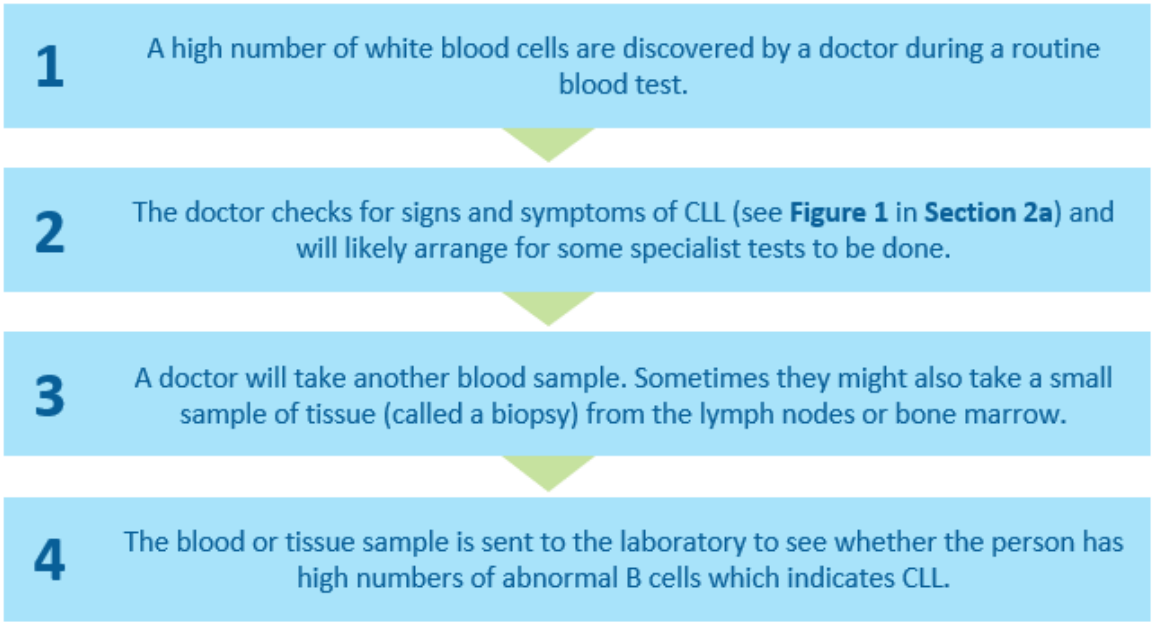
Family and friends often play a crucial role in caring for people with CLL.(1) As many people with CLL struggle to carry out everyday activities,(15) they may need full-time support from caregivers. Available evidence suggests that family members who care for a person with leukaemia (including CLL) have lower quality of life than people who do not take care of someone with CLL.(16) However, there are not many studies on this topic.

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

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

Sometimes people with CLL are already showing signs and symptoms of their condition when they are diagnosed. In these people, treatment will usually begin straight after diagnosis.(6) However, CLL will often be diagnosed before a person starts showing visible signs of the condition. If this is the case, a diagnosis of CLL often follows the process shown in **Figure 4**.(17)

Figure 4: Diagnosis of CLL



Abbreviation: CLL = chronic lymphocytic leukaemia

If CLL is confirmed, the doctor may try to understand how advanced the disease is. This is called the cancer stage. Determining a person's cancer stage can help to predict how a person's CLL could progress over time or respond to treatment.(18) The staging system commonly used in the UK is called the "Binet system". This is a three-step staging system based on the number of

swollen lymph nodes and blood test results (Table 1).(6, 10, 19) People with Stage C CLL are those with the most severe disease and worst outlook (prognosis).

Table 1: CLL cancer stages (Binet system)

CLL stage	Description
Stage A	Less than three areas of the body with swollen lymph nodes
Stage B	Three or more areas of the body with swollen lymph nodes but a normal number of other blood cells
Stage C	Three or more areas of the body with swollen lymph nodes and a low number of other blood cells

Abbreviation: CLL = chronic lymphocytic leukaemia

2c) Current treatment options:

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

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

Watch and wait

The term 'watch and wait' is sometimes used to describe the time between CLL diagnosis and treatment. Usually, people only receive treatment for CLL if it is Stage B or C and if the person is showing visible signs and symptoms of CLL. Until then, a person's CLL stage and symptoms will be monitored at regular check-ups with their doctor.(6, 20, 21) It has been estimated that the proportion of symptomatic (eligible to receive treatment at initial diagnosis) and asymptomatic ("watch and wait group") patients ranges from 26% to 34% and from 66% to 74%, respectively.(22)

Choosing the most appropriate treatment

If a person's CLL requires treatment, doctors usually choose the most appropriate option by looking at the genetic changes in the abnormal B cells and by considering the person's age and general health. It is also important that the person's own views are taken into account.(10)

Abnormalities in the B cells

Some medicines are less effective at treating CLL if the abnormal B cells have certain abnormalities. The most important abnormalities that doctors often look for are a missing part of chromosome 17 called 17p (17p deletion), changes in parts of a gene called TP53, and whether a part of the CLL cell called immunoglobulin heavy chain variable (IGHV) is mutated or unmutated.(6, 17)

Patient age and general health
Some medicines can cause more severe side effects in people with CLL who are older, frail and have other health conditions (comorbidities), such as heart, lung, kidney or liver conditions.(1, 17)

Personal preferences
People with CLL sometimes have their own preferences about treatment. For example, some people may prefer a treatment that is taken for a shorter time. Some people may prefer being able to take their medicine at home, whereas others may prefer to have their treatment in hospital surrounded by doctors and nurses. Similarly, some patients might prefer tablets, while others may choose to have medicines that are given by a drip into the blood (intravenously). There may also be certain side effects that some individuals would prefer to avoid.(10)

Current treatment options for previously untreated CLL

CLL cannot be cured, but there are a range of treatments currently used to try to improve the survival and quality of life of patients with CLL.(6) Treatments for CLL usually work by destroying abnormal B cells or stopping abnormal B cells from being made and multiplying. Most current first-line treatments for CLL are either a combination of chemotherapy and immunotherapy medicines (chemoimmunotherapy) or a targeted therapy, which might also have an immunotherapy added.

Chemotherapies work by destroying cells that grow and multiply quickly, which is common to all abnormal B cells. However, other cells in the body that multiply quickly (such as hair and skin cells) are also affected by chemotherapy. Therefore, these treatments often lead to side effects such as hair loss.(1) Chemotherapies are sometimes given by an intravenous drip or injection into the blood, which requires patients to receive these treatments in hospital.(23)

Immunotherapies work by helping a person's immune system to identify and destroy abnormal B cells.(23) Immunotherapies are often given by an intravenous drip or injection into the blood, but some can be taken as tablets.(24)

Targeted therapies work by blocking specific proteins that help abnormal B cells to survive or multiply.(23) They cause less severe side effects and are often more effective than chemotherapy and immunotherapy treatments.(25, 26) Targeted therapies used in CLL are given as tablets or capsules, which are less invasive and may not require people to go to hospital for their treatment.(27) Three main types of targeted therapies used for CLL are called Bruton's tyrosine kinase (BTK) inhibitors , B-cell lymphoma 2 (BCL-2) inhibitors and phosphoinositide 3-kinase (PI3K) inhibitors (**Figure 5**).(27)

Chemoimmunotherapy

Using more than one of these types of treatments 'in combination' allows them to work together to reduce the number of abnormal B cells more effectively and quickly.(1)

The main chemoimmunotherapy treatments used for CLL are:

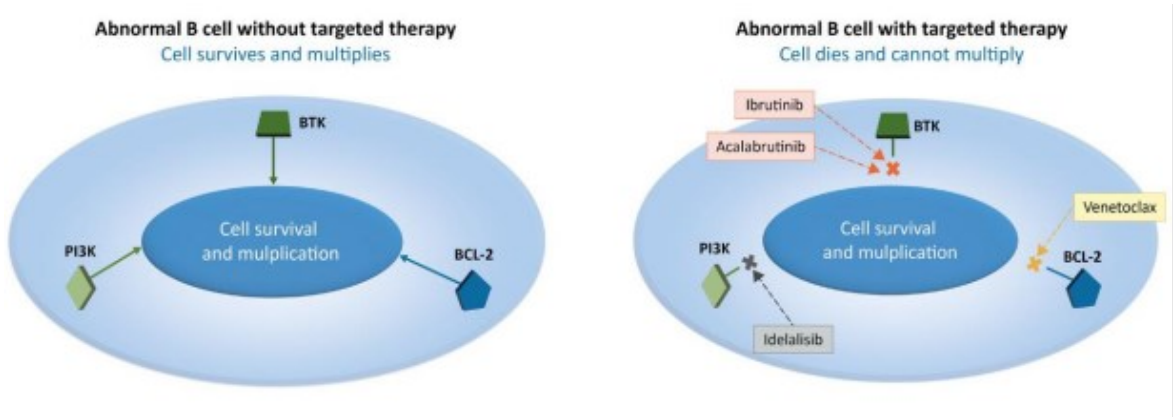
- Fludarabine, cyclophosphamide, and rituximab (FCR), which is usually only given to younger people who do not have other health conditions and who do not have 17p deletion, TP53 mutations or unmutated IGHV. This is because it can often cause severe side effects in elderly or frail patients and is not as effective at treating abnormal B cells.(28, 29)

- Bendamustine and rituximab (BR), which is sometimes used instead of FCR if people are over the age of 65 years.(6)
- Chlorambucil and obinutuzumab (O-Clb), which may be used among people who are older than 70 years or who have other health conditions.(26, 30)

Newer targeted therapies are often a better option for these patients as they can cause less severe side effects than chemo-immunotherapies.

Targeted therapies

Figure 5: Key targeted therapies for CLL



Abbreviations: BCL-2 = B-cell lymphoma 2; BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukaemia; PI3K = phosphoinositide 3-kinase

BTK inhibitors:

The most common BTK inhibitors used for CLL are ibrutinib and acalabrutinib. These treatments are suitable for most people with CLL. However, BTK inhibitors often cause side effects, such as a higher risk of infection, bruising and bleeding, changes to heartbeat, feeling sick and diarrhoea.(31) These treatments also have to be taken every day until a person's CLL worsens or the treatment causes too many side effects when taken alone or in combination with immunotherapies.

BCL-2 inhibitors:

The BCL-2 inhibitor used for CLL is venetoclax. Venetoclax is sometimes given in combination with an immunotherapy called obinutuzumab. However, this treatment can cause side effects, such as a low number of white blood cells, diarrhoea, feeling sick and tiredness. It can also cause a serious side effect called tumour lysis syndrome (TLS). More detail is provided on this later in section below).(30, 32)

PI3K inhibitors:

The PI3K inhibitor used for CLL is idelalisib. It is given in combination with an immunotherapy called rituximab. Idelalisib with rituximab in first-line is only recommended in people with TP53 or 17p changes, but can cause very severe side effects.(6, 33) It is therefore now rarely used in clinical practice and clinical experts agree that it has now been superseded by BTK inhibitors due to the higher risk of infection and death associated with idelalisib with rituximab.

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

Context:

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

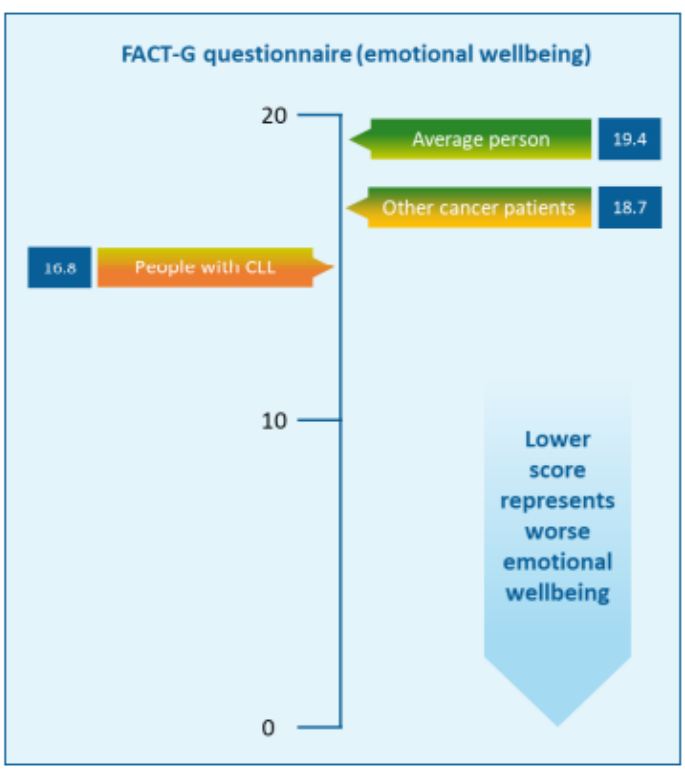
and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

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

CLL from the patient perspective

CLL can be both physically and mentally difficult for people living with the condition.(15) The symptoms of CLL can make it hard to carry out day-to-day activities, socialise, spend time with family members, exercise and function at work. In particular, the extreme tiredness caused by CLL has a negative impact on people with the condition. In patient interviews, one individual reported "I hadn't experienced fatigue like this – all my energy was going into work. I had to have some energy for my family, so I stopped working". Another person with CLL said "the fatigue meant I wasn't pleasant to be around, so I felt frustrated and guilty". Patients with CLL have reported worse emotional wellbeing compared to people without CLL and people with other types of cancer.(2) **Figure 6** shows the average emotional wellbeing scores for people with CLL, using a scale from 0 to 20, where higher scores indicate better emotional wellbeing.

Figure 6: Emotional wellbeing in people with CLL compared to those without the condition or with other types of cancer



Abbreviations: CLL = chronic lymphocytic leukaemia; FACT-G = Functional Assessment of Cancer Therapy - General

CLL from the carer perspective

Family members/partners play a key role in supporting patients and become "their second pair of eyes and ears" to listen out for information patients may miss, especially during consultations. One patient told us his "wife keeps a book of my symptoms and when we go see the specialist, I sit in a corner, and she talks to him". Another patient told us his "wife is more concerned than him and reminds him of doing certain things such as not going into crowded areas without a mask."

Caring for a patient with CLL can get challenging and stressful – because CLL patients may rely on them (transport to and from hospital appointments, reminders to take medicines, help with everyday activities).

The impact of CLL on quality of life varies between people

CLL affects quality of life in various ways. For example, it can affect people differently depending on their age. People older than 70 years often have worse overall quality of life than younger people and the condition has a particularly negative impact on their physical wellbeing. On the other hand, younger people with CLL can experience a greater impact on their social life, which leads to higher rates of anxiety and depression.(34) People with CLL who have other health conditions, such as heart or kidney issues, also tend to have worse quality of life and increased levels of anxiety.(2)

The impact of COVID-19

During COVID-19, people with CLL avoided leaving their homes because they were worried about their risk of infection.(35) The overall mental and emotional wellbeing of people with CLL, had likely been worsened by the COVID-19 pandemic. Surveys carried out by a UK patient organisation (CLL Support) throughout the pandemic found that more than 15% of patients were not coping well as a result of shielding against COVID-19 and around one in five patients had or were planning to seek help for their mental health during the pandemic.(36) A high number of patients reported being extremely worried about the outbreak.(36)

There are still some concerns among immunocompromised patients around the risk of infection, but the fear has likely diminished as the pandemic has slowed down.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

This treatment (I+V) combines ibrutinib and venetoclax, which already exist and are sometimes used on their own for treatment of CLL.

About ibrutinib

Ibrutinib is a BTK inhibitor, a type of targeted therapy which stops abnormal B cells from surviving and multiplying by blocking a protein called BTK in the cell.(37) Ibrutinib has already been approved by the European Medicines Agency (EMA) and other regulatory bodies for treating CLL and other types of cancer which affect B cells.(31) More than 250,000 patients have been treated with ibrutinib worldwide.(38)

About venetoclax

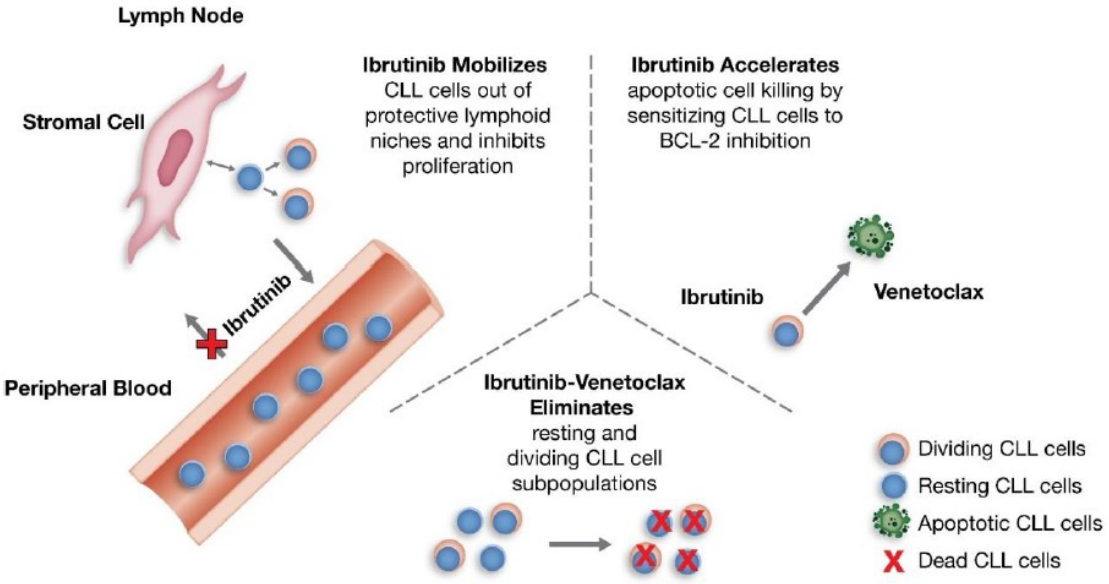
Venetoclax is a BCL-2 inhibitor, which is a different type of targeted therapy which stops abnormal B cells from surviving and multiplying by blocking a protein in the cell called BCL-2.(32) Venetoclax was first approved by the EMA in 2016 and has been used to treat CLL ever since.(32)

Ibrutinib in combination with venetoclax (I+V) is a new and innovative treatment for CLL

Using these two targeted therapies together is a new and innovative treatment option. This is because ibrutinib and venetoclax block two different proteins which help abnormal B cells to survive and continue to multiply (**Figure 5**). Therefore, when these medicines are used in combination, they work together to destroy abnormal B cells (**Figure 7**). I+V is currently being considered by the EMA as a first-line treatment for people with CLL.(31, 32)

Evidence suggests that I+V works more effectively at destroying abnormal B cells than O-Clb, a chemoimmunotherapy that is currently used to treat CLL. People who are given I+V are therefore likely to live longer without their CLL getting any worse, compared to people treated with O-Clb and have a similar quality of life.(39, 40)

Figure 7: Complementary mechanism of action of ibrutinib with venetoclax



CLL, chronic lymphocytic leukemia.

3b) Combinations with other medicines

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

- Yes / No

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

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

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

I+V is not intended to be used with any other CLL treatments.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Ibrutinib with venetoclax (I+V) is an all-oral fixed duration treatment

I+V is the only combination medicine for CLL that can be completely taken in tablet form. This means that, unlike many other CLL treatments, patients do not have to be given I+V by an intravenous drip or injection into the blood. Once patients are on the full dose of venetoclax, they will not need to travel to hospital to receive their treatment.(41, 42) This can be better for people with CLL who find medicines injected into the vein uncomfortable or unpleasant. It can also mean that patients and their caregivers do not need to travel to and from the hospital as regularly. This can save time and money and help to maintain a sense of normality during their treatment.

I+V is also only taken for a fixed period of time and then stopped (fixed duration). This is unlike some continuous CLL treatments that are only stopped when the medicine stops working or if patients experience side effects that are too severe.

How much medicine do patients take and when?

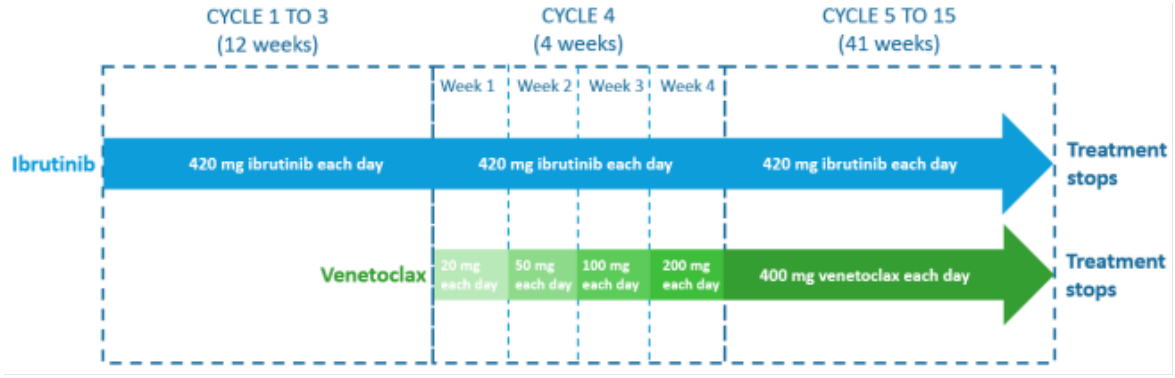
For **ibrutinib**, patients take one tablet containing a total of 420 mg. Ibrutinib tablets should be taken at the same time every day, if possible. Tablets should be swallowed whole with a glass of water and should not be opened, chewed or broken before they are taken. If a patient forgets to take ibrutinib, they should take the tablet as soon as they remember on the same day. The next dose should then be taken as usual on the next day. Patients should not take more tablets than are needed for one dose at the same time to make up for any doses that were missed.(31)

After patients have been taking ibrutinib for three cycles (see below), they will start taking **venetoclax** tablets as well.(43) To start, patients will be given a dose of 20 mg. This dose will then be gradually increased each week until it reaches 400 mg. During cycle 4, patients may need to take the oral-based venetoclax in a hospital setting for monitoring of side effects such as TLS, whilst the dose is gradually increased each week until it reaches 400mg. Tablets should be swallowed whole with a glass of water and taken with a meal, and should not be opened, chewed or broken before they are taken. The total length of time from the start of ibrutinib treatment to the end of the I+V combination is 15 cycles (**Figure 8**).(32, 43)

What is a cycle?

Many cancer treatments are given in cycles. Each cycle is usually split into a period where patients receive a treatment, followed by a period where the treatment is stopped to allow their body to recover. The length of each cycle and the split between treatment and rest periods can depend on the type of treatment and on the patient.(44) For I+V, most patients would be on cycles lasting **28 days** (four weeks).(40)

Figure 8: Ibrutinib with venetoclax (I+V) administration schedule



3d) Current clinical trials

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

Table 2 summarises clinical trials which study patients treated with I+V. As of June 2022, there are two trials that are both ongoing. However, some of the key results from these trials are already available and both trials are explained in more detail below.

Table 2: Trials investigating ibrutinib with venetoclax (I+V)

Phase (clinical trial name and number)	Location	CLL patient group	Number of patients included	Expected completion date
Phase 2 (CAPTIVATE, NCT02910583)(45)	Europe North America Asia-Pacific	No prior treatment	323	2023
Phase 3 (GLOW, NCT03462719)(46)	Asia Europe North America	No prior treatment	211	2024

Abbreviation: CLL = chronic lymphocytic leukaemia

3e) Efficacy

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

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

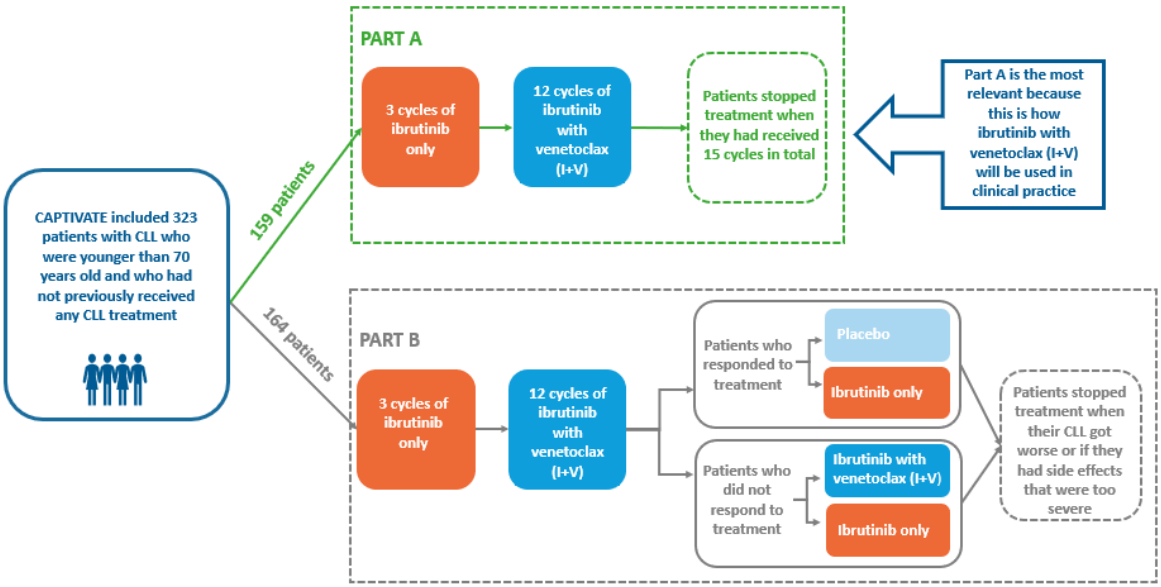
Two clinical trials studied I+V for the first-line treatment of CLL, the CAPTIVATE trial and the GLOW trial. CAPTIVATE is a phase II trial, which means that it tests whether I+V is safe to use in people with CLL and how well it works to destroy abnormal B cells (its efficacy). GLOW is a phase III trial, which means that it compares the efficacy and safety of I+V to another common CLL treatment. In this case, GLOW compares I+V with O-Clb. GLOW also looks at the impact of I+V on patients' quality of life.(47, 48)

How were the trials carried out?

Figure 9 shows how CAPTIVATE was carried out. Patients in Part A received I+V for a fixed period of time and then stopped treatment. Patients in Part B received I+V for different periods of time,

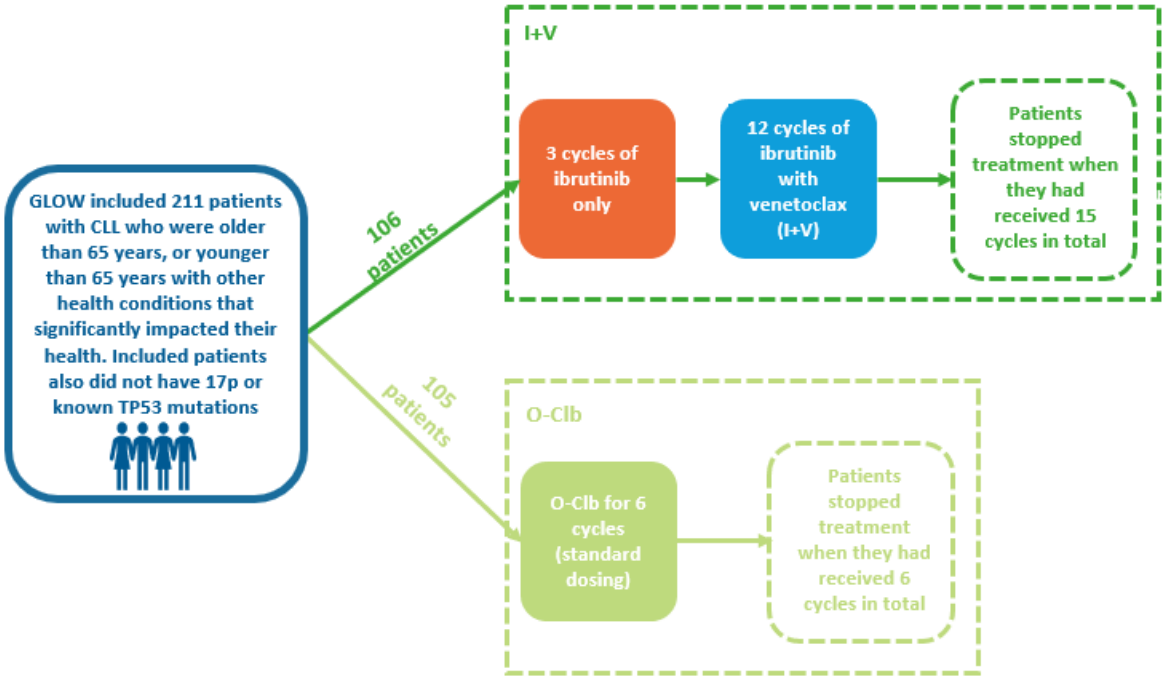
depending on their response to the first mandatory period of treatment time.(48) Part A used I+V in the same way that it will be given to patients in clinical practice. Therefore, only the results of Part A will be explained. A summary of how GLOW was carried out is provided in **Figure 10**. In GLOW, patients either received I+V (administered in the same way as Part A in CAPTIVATE) or O-Clb.

Figure 9: Summary of how CAPTIVATE was carried out



Abbreviation: CLL = chronic lymphocytic leukaemia

Figure 10: Summary of how GLOW was carried out

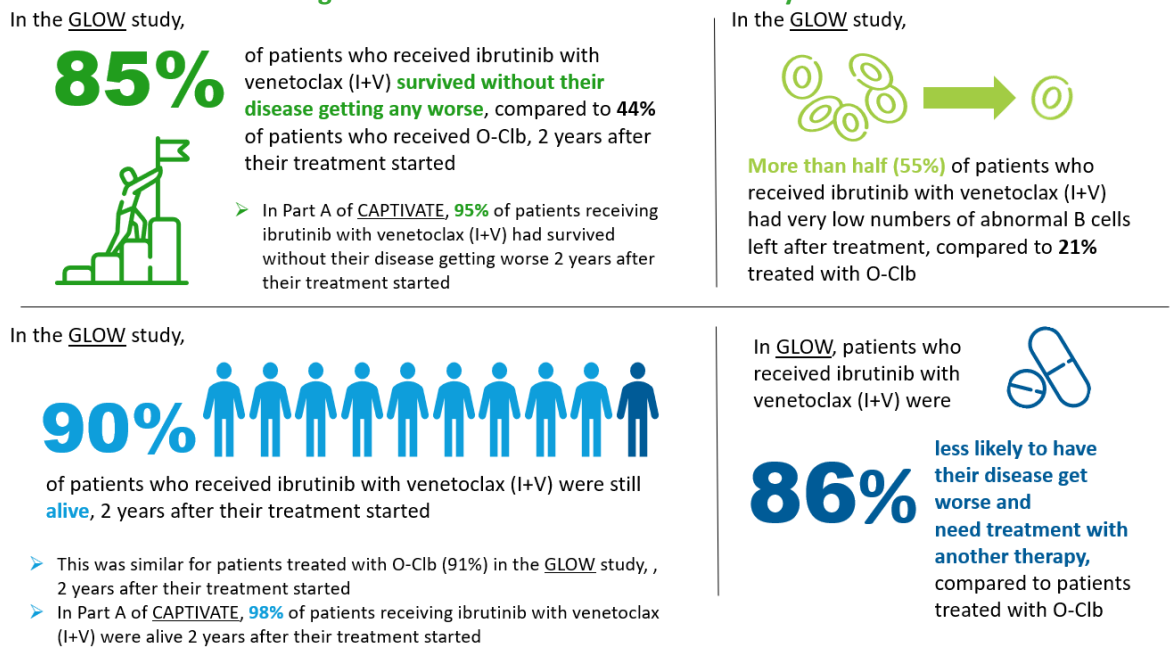


Abbreviations: CLL = chronic lymphocytic leukaemia; I+V = ibrutinib plus venetoclax; O-Clb = obinutuzumab plus chlorambucil

Trial results

The results of CAPTIVATE and GLOW after two years after start of treatment are shown in **Figure 11**. As a larger and phase III trial, the figure focuses on results from GLOW, with CAPTIVATE results used to support any key findings.

Figure 11: GLOW and CAPTIVATE efficacy results



Abbreviation: O-Clb = obinutuzumab and chlorambucil

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

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

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

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

In CAPTIVATE, information about patients' quality of life was not collected.

Throughout GLOW, patients were asked to answer questions about their quality of life. They were also asked about their levels of extreme tiredness (fatigue), as this is a symptom known to impact quality of life for people with CLL.(39)

Regardless of whether patients were given I+V or O-Clb, treatment led to similar improvements in quality of life. There was no overall worsening of quality of life despite the longer duration of I+V vs. O-Clb. Both treatments improved fatigue levels.(39)

3g) Safety of the medicine and side effects

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

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had

treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Each medicine has its own side effects, and the same medicine can produce different reactions in different people. Side effects were reported in both groups of patients, as shown in **Table 3**. Some patients stopped taking the treatments because of the side effects they experienced.(39) The most common side effects experienced by patients receiving I+V were diarrhoea and a low number of white blood cells. A low number of white blood cells was also common in patients receiving O-Clb. The other most common side effect in the O-Clb group was reactions to medicines that are given by a drip or injection into the bloodstream.(39)

Table 3: GLOW safety results

		Percentage of patients showing side effect	
	Side effect	Ibrutinib with venetoclax (I+V)	O-Clb
	Any side effect	**99.1%**	**94.3%**
	Serious side effect	**46.2%**	**27.6%**
	Stopped taking the treatment because of side effects	**10.4%**	**1.9%**
Common side effects (more than 20% of patients in either treatment group)	**Low number of white blood cells** *(can cause increased risk of infection)*	34.0%	53.3%
	Low number of platelets *(can cause patients to bleed easily)*	26.7%	11.3%
	Nausea *(can cause discomfort in the stomach and an urge to vomit)*	26.4%	25.7%
	Diarrhoea *(loose or watery stools more than three times a day)*	50.9%	12.4%
	Reaction to intravenous drip administration *(can cause nausea, headache, fast heartbeat, rashes and shortness of breath)*	0%	29.5%
Most common serious side effects (more than 2% of patients in at least one treatment group)	**Infection of the lungs** *(can cause chest pain when breathing, cough, extreme tiredness, fever)*	5.7%	5.7%
	Atrial fibrillation *(irregular and very fast heartbeat)*	6.6%	0%
	Febrile neutropenia *(can cause a fever, chills or sweating, sore throat, stomach pain, shortness of breath)*	1.9%	2.9%

Abbreviation: O-Clb = obinutuzumab and chlorambucil

Managing side effects

The most common side effects of I+V are low number of white blood cells and diarrhoea, which can be managed by delaying dosing schedules and changing the doses of treatment.

Both venetoclax and obinutuzumab are associated with a risk of TLS, requiring monitoring and taking action to prevent this from happening. TLS happens when lots of cancer cells are destroyed very quickly. As cancer cells break down, they release a chemical called uric acid, which is removed from the body by the kidneys. When cancer cells get destroyed very quickly, the kidneys cannot cope with the increased amount of uric acid. This leads to imbalances in some chemicals (phosphate, potassium and calcium) in the blood. These imbalances can cause serious problems affecting the kidneys and the heart.

In the GLOW trial, there were no cases of TLS reported in the I+V arm compared with six cases (5.7%) reported in the O-Clb arm. Taking ibrutinib for the first 3 cycles as part of the I+V regimen is called the "3 cycle lead-in" (**Figure 8**). After three cycles of ibrutinib lead-in, two patients (1.9%) remained at high tumour burden per tumour lysis risk category, reduced from 26 (24.5%) at baseline.

Abbreviation: TLS = tumour lysis syndrome

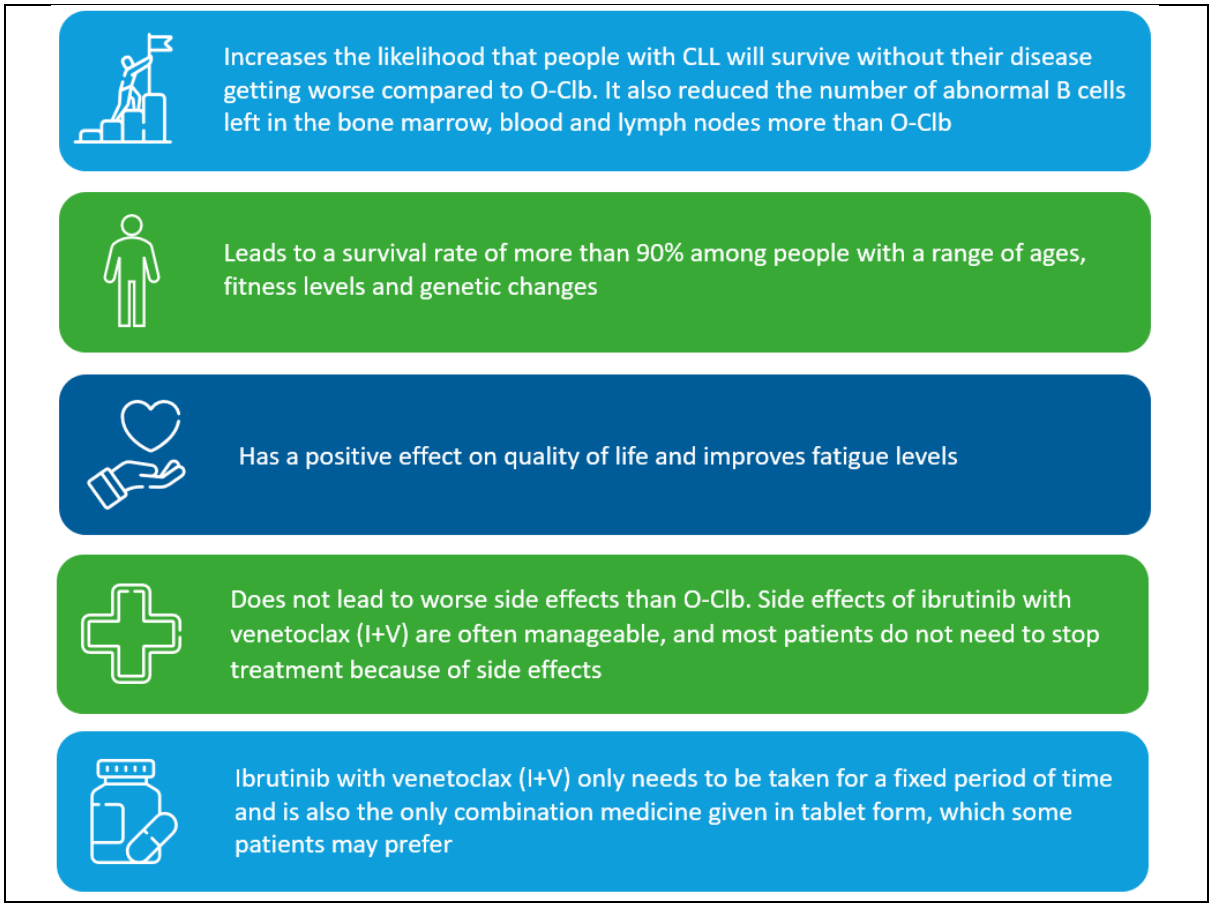
3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Trials have primary endpoints – which is the main results measured at the end of the study to see if the treatment worked. The primary endpoint for CAPTIVATE was to measure how well patients responded to I+V. The primary endpoint for GLOW was to measure how much longer patients stay progression-free on I+V compared with O-Clb.

Based on the results of CAPTIVATE and GLOW, we have found that two years after treatment is started, I+V:(39, 43)



3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:
• Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments
• Overall, the side effects observed in patients treated with I+V from the two trials (CAPTIVATE and GLOW) are in line with what is expected with ibrutinib and venetoclax when they are taken on their own. • Patients taking I+V reported a higher rate of diarrhoea and low number of white blood cells, compared to ibrutinib alone.   ○ Most diarrhoea cases were low in severity.

3j) Value and economic considerations

Introduction for patients:

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

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

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

Introduction for patient groups

Healthcare administrators need to get the most value from their limited budgets. To do this, they are interested in knowing whether a new medicine provides 'good value for money' compared to other medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a health economic model.

How the model reflects the condition

- The economic model assigns patients to different treatments (I+V or currently available treatment options) and sums up the costs and quality of life over the patients' lifetimes
- The goal of the model is to compare the costs and quality of life of patients treated with I+V compared to currently available treatment options
- If I+V maximises survival and quality of life for the amount of money it costs, I+V is considered a "good use of National Health System (NHS) resources"
- The model includes the first treatments which CLL patients receive, but also the treatments they receive after progression, to accurately reflect what happens in reality

Modelling how much a treatment extends life

- Trials collect information about a treatment for a limited time period
- In the model, this data needs to be extrapolated over a longer period of time to predict total outcomes over a patient's lifetime
- The main outcomes that are used in the model are how long patients stay alive without their disease becoming worse (progression-free survival), how long patients stay alive (overall survival) and side effects of treatments
- From the model, it can be concluded that I+V helps patients stay progression-free for longer, compared to other treatment options

Modelling how much a treatment improves quality of life

- Patients from the GLOW trial were asked about their quality of life at the start of the trial, whilst they were on treatment, and shortly after stopping treatment
- Their responses were collected using questionnaires, and this informed quality of life of CLL patients when they are receiving first line treatment and are progression-free
- In other instances, when GLOW data was not sufficient, further information about quality of life of CLL patients was sourced from literature

Modelling how the costs of treatment differ with the new treatment

- I+V is cheaper than most existing treatments (O-Clb, venetoclax + obinutuzumab and acalabrutinib) when costs over lifetime are added together
- I+V is slightly more expensive than chemoimmunotherapy FCR when costs over lifetime are added together; however, this is balanced by the increased survival and quality of life provided by I+V

Uncertainty

- When data from clinical trials are extrapolated beyond the end of observed data (follow-up period), there is uncertainty in the predicted outcomes
- Where possible, the predicted outcomes have been checked against other available sources (real-world evidence and other clinical trials) to see if they are plausible and reflect the expected clinical reality
- Data about some costs or outcomes are sometimes not available. In that case, assumptions are used in the model, which are also varied to see the impact on the results

What is the value of I+V for patients, carers and the health service?

As CLL has a negative impact on patients, their carers and the healthcare system, there is a demand for new and effective treatment options that can reduce the burden associated with CLL.(3, 11) I+V has been shown to have high efficacy in treating CLL.(40, 49) It is also the only combination medicine that can be taken completely in tablet form.(49) Among other benefits, this reduces the need for patients to travel to and from hospital to receive their treatment, which may be more convenient for patients.(50) It also saves important resources in hospitals, such as injection equipment and the time of nurses, pharmacists and doctors.

Economic analysis

All these considerations affect whether I+V represents good value for money and a good use of NHS resources. Based on the evidence that is available and the economic analysis results, I+V is considered a good use of NHS resources as a new first-line treatment option for patients with CLL.

Benefits of I+V not captured in economic model

The key benefit of I+V not captured by economic model is its potential to reduce medicalisation compared with current treatment options. Medicalisation is the process whereby patients begin to define themselves by their disease, for example, patients having to plan life around frequent hospital visits and anticipate that their entire remaining life will be spent on treatments with various side effects. This is especially burdensome for elderly CLL patients who are more frequently reliant on other people for transport to and from hospital (medicalising the lives of even healthy individuals). Younger patients with CLL can be affected by this medicalisation process too – for example, parents of young children must repeatedly arrange childcare and time off work to receive treatment.

I+V offers a step-change in the medicalisation process for CLL. It is the only combination medicine that can be taken completely in tablet form. Among other benefits, this reduces the need for patients to travel to and from hospital to receive their treatment, which may be more convenient for patients.

I+V is given for a fixed time period; therefore, patients have both a shorter exposure compared to other treatments which are given until their disease gets worse and potentially a lengthy ‘treatment holiday’ between finishing the treatment and their disease becoming worse and needing another CLL treatment. While a ‘treatment holiday’ may not be important to all patients,

for those patients for whom it is important it will not be captured in the economic model while in fact having a significant positive impact on their non-health quality of life.

3k) Innovation

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

Ibrutinib in combination with venetoclax is a new and innovative treatment for CLL

I+V is innovative as it is the first combination of targeted therapies in CLL. I+V combines the activity of two targeted agents, and they work in a complementary way. Ibrutinib and venetoclax block two different proteins that help abnormal B cells to survive and continue to multiply (**Figure 7**). Therefore, when these medicines are used in combination, they work together to destroy abnormal B cells.

I+V is currently being considered by the EMA as a first-line treatment for people with CLL. (31, 32) Clinicians value the opportunity to administer a combination of effective agents upfront to minimise the possibility of patients' disease getting worse.

3l) Equalities

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

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

There is an urgent need for younger, fitter patients with CLL to have access to new treatments as currently only FCR or venetoclax + obinutuzumab is available to them. I+V will address this inequality in opportunity.

SECTION 4: Further information, glossary and references

4a) Further information

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

Further information on CLL

- https://www.nhs.uk/conditions/chronic-lymphocytic-leukaemia/
- https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll
- https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html

Further information on ibrutinib

- https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/ibrutinib

Further information on the CAPTIVATE trial:

- https://www.clinicaltrials.gov/ct2/show/NCT02910583
- https://pubmed.ncbi.nlm.nih.gov/34618601/

Further information on the GLOW trial

- https://clinicaltrials.gov/ct2/show/NCT03462719
- https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200006

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Advanced	Advanced is used to describe cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to other parts of the body.
B cells (also called B lymphocytes)	B cells are a type of white blood cell in the immune system that help to fight infections.
B-cell lymphoma 2 (BCL-2) inhibitors	These are a type of targeted therapy that block a protein called BCL-2, which helps abnormal B cells to survive and continue to multiply.
Bone marrow	This is a soft, spongy tissue inside most bones where blood cells (e.g., red blood cells, white blood cells and platelets) are made.
Bruton's tyrosine kinase (BTK) inhibitors	These are a type of targeted therapy that block a protein called BTK, which helps

	abnormal B cells to survive and continue to multiply.
Chromosome	These are long, threadlike structures of DNA that are present in every cell. DNA is the genetic code that is in the heart of all animal and plant cells. It controls everything the cell does.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.
Comorbidities	This is when more than one illness or disease is present in one person at the same time.
Continuous	This means that your treatment is continued indefinitely and is only stopped if your treatment stops working or if you develop side effects that are difficult to cope with.
Cycles	Many cancer treatments are given in cycles. Each cycle is often divided into a period where you receive a treatment, followed by a period of rest from treatment to allow your body to recover from the side effects of treatment. The length of each cycle and the split between treatment and rest periods can depend on the type of cancer you have, where it is in your body and if it has spread and where to. For ibrutinib with venetoclax (I+V), most patients would be on a cycle lasting 28 days (four weeks).
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.
European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.
Fatigue	This is when you feel very tired, exhausted and lacking energy. It can be a symptom of the cancer itself or a side effect of treatment
First-line treatment	This is the first treatment given for your disease or illness
Fixed duration	This means that your treatment is only taken for a fixed length of time and then stopped. It is the opposite to a continuous treatment (see 'continuous' definition)
Genetic changes	Our genes pick up mistakes that happen when cells divide. These mistakes are called genetic changes or mutations. It is usual for cells to repair faults in their genes or to be removed by the body. Cancer happens when cells with genetic changes are not repaired or removed

	from the body and instead multiply out of control.
Health economic model	A tool used to predict the costs and effects of a technology over a length of time or in patient groups not covered in a clinical trial.
Health Technology Assessment (HTA)	An assessment about the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared with existing ones. Reimbursing involves the payment that your hospital, doctor, diagnostic facility, or other healthcare providers receive for giving you a medical service.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
In combination	This is when you are given more than one medicine at the same time to treat your cancer.
Intravenous drip	Some cancer drugs are diluted in a bag of fluid, and you have them as drip. The drip bag is connected to a cannula and the drug goes into your vein.
Intravenously	This when you are given medicine through an injection or drip (see 'intravenous drip') into your vein.
Invasive	A medical procedure that enters the body, often by cutting or puncturing the skin or inserting instruments into the body.
Lymph nodes (also called glands)	Small structures in the body that trap germs and abnormal cells. Found in the neck, armpit and groin.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country
Monotherapies	Therapies that use one type of treatment to treat a certain disease or illness. In drug therapy, monotherapy refers to the use of a single drug to treat a disease or condition.
Phase 1 (also called phase I) clinical trial Small number of patients – less than 100 – who have not been helped by other treatments.	This is the first step in testing a new treatment in people. A phase I clinical trial tests: • the safety, side effects, best dose, and timing of a new treatment, • the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection), and • how the treatment affects the body The dose is usually increased a little at a time to find the highest dose that does not cause harmful side effects.

Phase 2 (also called Phase II) clinical trial Small number of patients – less than 100– who have not been helped by other treatments.	A study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumour or improves blood test results). Phase II clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body.
Phase 3 (also called Phase III) clinical trial May include hundreds of people.	This phase tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III clinical trials only after they meet the goals of phase I and phase II clinical trials.
Phosphoinositide 3-kinase (PI3K) inhibitors	These are a type of targeted cancer drug that block a protein called PI3K inside cancer cells which tell the cancer to grow.
Prognosis	This gives an idea about whether the cancer can be cured and what may happen in the future.
Proteins	These are structures inside all cells of our body that are important for many activities, including growth and repair.
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Regulatory bodies	These are legal bodies that review the safety and efficacy of medicines and medical technologies.
Risk factors	These are things that can increase your risk of getting a disease. These factors can be from your genes, lifestyle and environment.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment with a medication or other therapy. Side effects may be mild, moderate, or severe.
Spleen	An organ in the rib cage that helps filter blood and helps fight infection.
Stage	A description of how severe a disease is.
Targeted therapy	Targeted cancer drugs work by 'targeting' those differences that help a cancer cell to survive and grow, while limiting damage to healthy parts of the body.
Tolerated	The ability to put up with the side effects of treatment.

White blood cell	They are cells in the body that fight disease and infection by attacking and killing germs.

4c) References

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Clarification questions

October 2022

File name	Version	Contains confidential information	Date
ID3860_ibrutinib_clarification_response_Janssen_FINAL_ACIC	FINAL	Yes	21st October 2022

Tables

Figures

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Document B, Section B.2.1, Identification and selection of relevant studies, and Appendix D.1.6.1. The company submission indicates that 92 publications reporting 17 RCTs met the SLR inclusion criteria. Appendix D.1.6.1, Tables 11-14, which report findings from these 17 RCTs, cite only around 28 references (publications). Please clarify how the remaining 64 publications that met the SLR criteria were used in the submission.

All (92) publications pertaining to the relevant trials (including abstracts and full-text articles) which met the defined selection criteria were included in the systematic literature review (SLR), as detailed in the PRISMA diagram presented in Figure 1 on page 26 of the ID3860 Appendices. However, when summarising the relevant information from these studies, the data from each trial were consolidated, particularly to avoid double-counting unique groups of patients. This involved capturing first information from the primary publication for any given study, and then adding and citing data from any preceding abstracts or subsequent related publications (abstracts or full texts) only where evidence was not available, or superseded data, from the primary publication (e.g., additional subgroup data and results from later timepoints). The majority of non-primary publications for the 17 unique trials did not provide such information, so while they are recognised as having been identified in the SLR, they are not cited in Tables 11 to 14 of the ID3860 Appendices, because doing so could give the misleading impression that they provide unique data for the study concerned.

In summary, only 28 references are cited as these publications provided the most information about each of the relevant trials, and superseded information provided in the remaining 64 publications. This approach prevents double-counting groups of patients.

A2. Document B, section B.2.5 and Appendix D.2.3. These sections of the company submission refer to the quality assessment of the CAPTIVATE and GLOW studies. Please clarify how many reviewers carried out the studies' risk of bias

assessment and whether they worked independently. Please also clarify how many reviewers carried out data extraction and whether they worked independently.

Quality assessment was independently carried out by one investigator and information was validated by a second investigator. A third investigator was consulted to resolve disagreements as necessary.

The data extraction was performed to the same methodological standards as the quality assessment. Data was first extracted independently into a data extraction form by one investigator, and the accuracy and completeness of the extracted data was subsequently validated by a second investigator. Any discrepancies were resolved by a third independent investigator.

Clinical effectiveness results

A3. Document B, section B.2.10.1. Adverse events for the FD cohort of the CAPTIVATE study but not for the MRD cohort are reported in the main submission document. Please clarify why adverse events for the MRD cohort have not been reported.

Patients in the fixed duration (FD) cohort of the CAPTIVATE study received ibrutinib monotherapy (420 mg/day orally) as a lead-in treatment for three cycles, a dose ramp-up for venetoclax (from 20 mg/day to 400 mg/day orally over 5 weeks) from Cycle 4 and continued treatment with venetoclax (400 mg/day orally) in combination with ibrutinib (420 mg/day orally) for 12 cycles until Cycle 15.(1) This is in line with the I+V regimen in the submission and expected clinical use.

However, patients in the MRD cohort of the CAPTIVATE study received an additional cycle of I+V (Cycle 16) while MRD status was confirmed and tumour response was assessed, followed by subsequent treatment with I+V, ibrutinib monotherapy or placebo depending on MRD status.(2) This is a different treatment regimen from the expected clinical use. Thus, only adverse events (AEs) from the FD cohort of the CAPTIVATE study are reported in the main submission document and informed the economic analysis, rather than AEs from the MRD cohort.

However, since the MRD cohort can still provide valuable additional safety data on I+V in a population of patients with previously untreated CLL and Janssen are keen to provide a comprehensive overview of any safety data, any grade and grade ≥3 TEAEs from a pooled safety cohort (FD cohort + first 16 cycles of the MRD cohort; N=323) are presented in Table 1 below alongside the FD cohort (N=159).

Of note, no additional safety concerns were identified with the inclusion of safety data from the MRD cohort and the overall incidence of any grade and grade ≥3 TEAEs were similar.(1) Any grade and grade ≥3 TEAEs in the MRD cohort (without the FD cohort) after the first 16 cycles of treatment and as of the primary analysis (median 27.9 months follow-up) are presented in Table 14.3.1.3.2 on page 1,233 of the CAPTIVATE clinical study report (CSR).(3)

Table 1 Summary of TEAEs by system organ class and preferred term in the CAPTIVATE FD and pooled safety cohorts

TEAEs by preferred term, n (%)	FD cohort (N=159)		Pooled safety cohort (FD cohort + first 16 cycles of the MRD cohort; N=323)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Gastrointestinal disorders	[redacted]	[redacted]	289 (89.5)	25 (7.7)
Diarrhoea	99 (62.3)	5 (3.1)	215 (66.6)	13 (4.0)
Nausea	68 (42.8)	2 (1.3)	142 (44.0)	2 (0.6)
Vomiting	35 (22.0)	[redacted]	70 (21.7)	4 (1.2)
Dyspepsia	29 (18.2)	[redacted]	57 (17.6)	---
Constipation	25 (15.7)	[redacted]	52 (16.1)	---
Mouth ulceration	24 (15.1)	[redacted]	38 (11.8)	---
Stomatitis	21 (13.2)	[redacted]	45 (13.9)	2 (0.6)
Infections and infestations	106 (66.7)	13 (8.2)	225 (69.7)	27 (8.4)
Upper respiratory tract infection	37 (23.3)	[redacted]	85 (26.3)	---
Cellulitis	11 (6.9)	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	215 (66.6)	9 (2.8)
Rash maculo-papular	27 (17.0)	[redacted]	50 (15.5)	4 (1.2)
Petechiae	17 (10.7)	[redacted]	37 (11.5)	---
Pruritus	17 (10.7)	[redacted]	[redacted]	[redacted]
Dry skin	16 (10.1)	[redacted]	35 (10.8)	---
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	214 (66.3)	13 (4.0)
Arthralgia	53 (33.3)	2 (1.3)	109 (33.7)	6 (1.9)
Muscle spasms	47 (29.6)	[redacted]	79 (24.5)	---
Myalgia	23 (14.5)	[redacted]	47 (14.6)	---
Back pain	21 (13.2)	[redacted]	47 (14.6)	4 (1.2)
Pain in extremity	21 (13.2)	[redacted]	43 (13.3)	1 (0.3)
Blood and lymphatic system disorders	[redacted]	[redacted]	202 (62.5)	116 (35.9)
Neutropenia	66 (41.5)	52 (32.7)	136 (42.1)	110 (34.1)
Increased tendency to bruise	35 (22.0)	[redacted]	70 (21.7)	---
Thrombocytopenia	21 (13.2)	[redacted]	51 (15.8)	10 (3.1)
General disorders and administration site conditions	[redacted]	[redacted]	166 (51.4)	8 (2.5)
Fatigue	39 (24.5)	1 (0.6)	85 (26.3)	5 (1.5)
Pyrexia	21 (13.2)	---	42 (13.0)	---
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	157 (48.6)	4 (1.2)
Cough	27 (17.0)	---	55 (17.0)	---
Epistaxis	18 (11.3)	---	42 (13.0)	---
Oropharyngeal pain	17 (10.7)	---	45 (13.9)	---
Nervous system disorders	[redacted]	[redacted]	143 (44.3)	10 (3.1)
Headache	40 (25.2)	[redacted]	86 (26.6)	2 (0.6)
Dizziness	26 (16.4)	[redacted]	52 (16.1)	---

TEAEs by preferred term, n (%)	FD cohort (N=159)		Pooled safety cohort (FD cohort + first 16 cycles of the MRD cohort; N=323)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Injury, poisoning and procedural complications	[redacted]	[redacted]	116 (35.9)	3 (0.9)
Contusion	24 (15.1)	---	55 (17.0)	---
Metabolism and nutrition disorders	[redacted]	[redacted]	118 (36.5)	14 (4.3)
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	101 (31.3)	21 (6.5)
Neutrophil count decreased	16 (10.1)	8 (5.0)	20 (6.2)	11 (3.4)
Vascular disorders	[redacted]	[redacted]	72 (22.3)	24 (7.4)
Hypertension	25 (15.7)	9 (5.7)	51 (15.8)	22 (6.8)
Cardiac disorders	[redacted]	[redacted]	70 (21.7)	11 (3.4)
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]

FD = fixed duration; I+V = ibrutinib + venetoclax; MRD = minimal residual disease; TEAE = treatment-emergent adverse event
Source: Pharmacyclics [Data on File], 2021(3); Tam, 2022(4); ClinicalTrials.gov, 2022(5); EMA, 2022(1)

A4. Document B, section B.2.9.2. A matching-adjusted indirect comparison (MAIC) for the fludarabine + cyclophosphamide + rituximab (FCR)-unsuitable population is described in the company submission, but the weights have not been provided. Please clarify what weighting approach was employed and the effects of the calculated weights on the study differences. Please also clarify the uncertainties around these weights.

In the absence of head-to-head studies comparing I+V vs. venetoclax + obinutuzumab (VenO) and acalabrutinib, indirect treatment comparisons (ITCs) are required to estimate the relative treatment effects between these treatments. Since patient-level data is only available for the GLOW trial, a MAIC can be used to estimate relative efficacy between the treatments.(6)

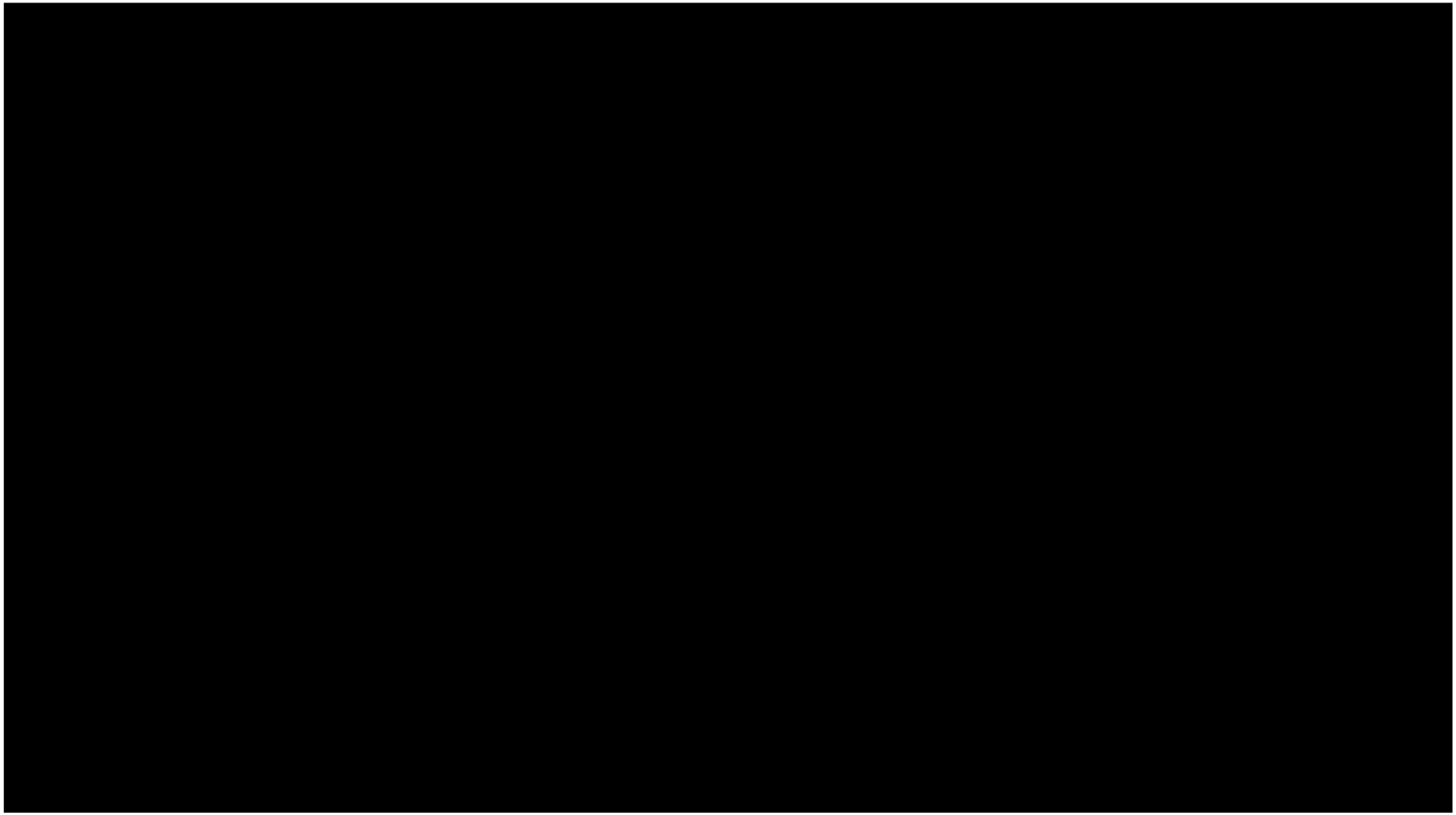
The MAIC technique relies on weights assigned to patients in the index trial (GLOW in this case) to balance differences in baseline characteristics with those of the comparator trials: CLL14 and ELEVATE-TN. The weights were derived using the method of moments (as individual patient data [IPD] is not available for the comparators) in such a way that the reweighted profile matches the population of the comparator study on all common characteristics without overmatching (see Table 2 and Table 3).

To properly take uncertainty into account, the robust sandwich estimator is used to estimate the standard errors.(6)

The histograms of weights distribution and the weights applied to the I+V vs. acalabrutinib and vs. VenO MAICs in the FCR-unsuitable population are provided in Appendix 1 and Appendix 2 of the separate appendix document, respectively.

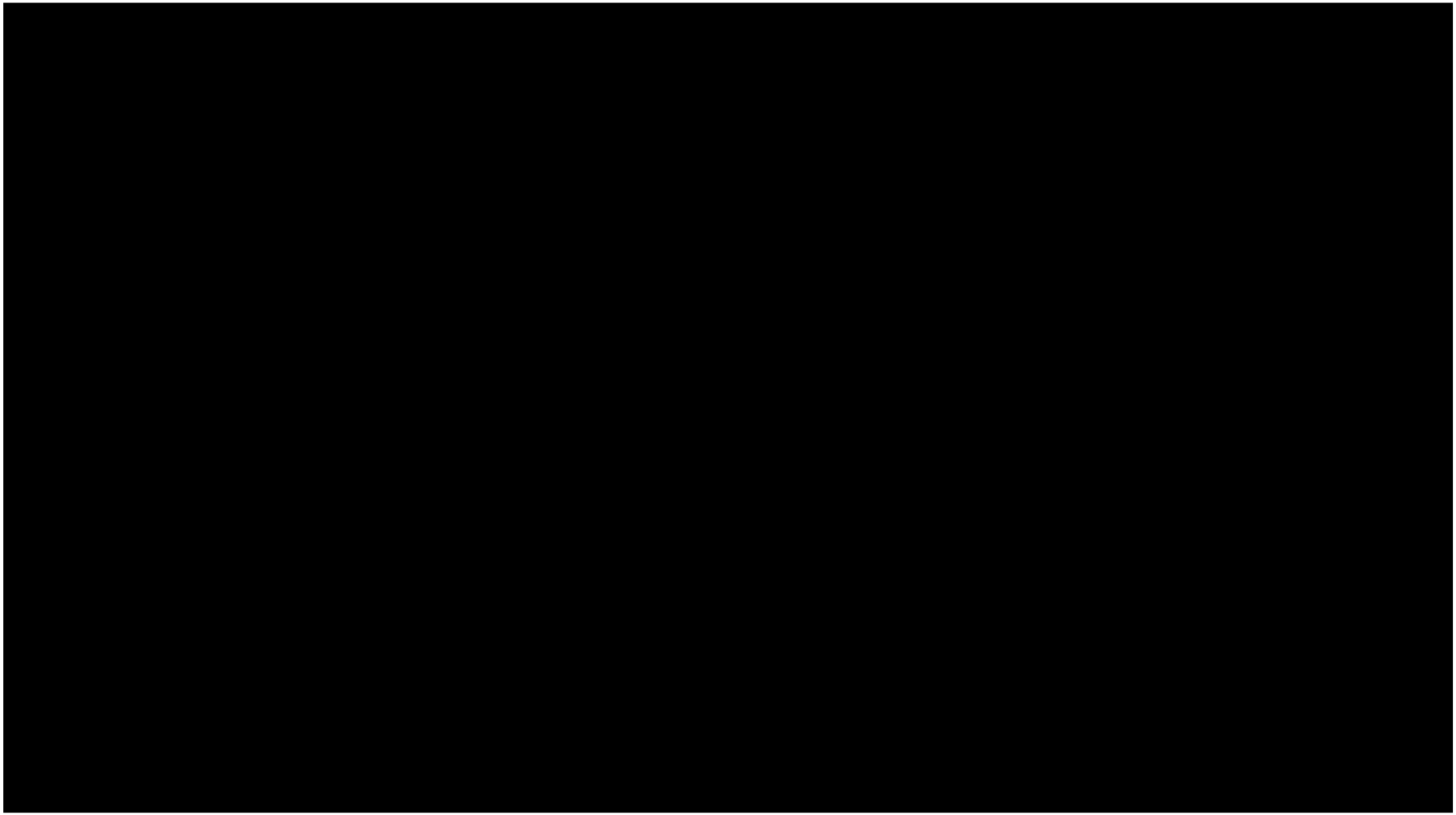
The tables below provide the GLOW (I+V) baseline characteristics before and after matching to CLL14 (VenO; Table 2) and ELEVATE-TN (acalabrutinib; Table 3).

Table 2 GLOW baseline characteristics before and after matching to CLL14 study



ECOG = European Cooperative Oncology Group; IGHV = immunoglobulin heavy chain variable region; TP53 = tumour protein 53

Table 3 GLOW baseline characteristics before and after matching to ELEVATE-TN study



CIRS-G = Cumulative Illness Rating Scale-Geriatric; del11q = 11q deletion; ECOG = European Cooperative Oncology Group; IGHV = immunoglobulin heavy chain variable region; TP53 = tumour protein 53

Section B: Clarification on cost-effectiveness data

Model Structure

B1. Section B.2.3. It is noted that tunnel states are used to capture and follow each cohort of patients entering the PF 2L state. Yet, later in the submission, it is stated that the exponential distribution is used to model PFS in PF L2 because the model cannot track the survival of patients stratified by the cycle of progression. Please clarify the purpose of the tunnel states and what they are used for.

The tunnel states functionality was used to capture the costs of subsequent treatment more accurately in the economic model. Subsequent treatment costs per cycle are not constant and dependent on time as patients can be on FD or treat to progression therapies. Therefore, costs are applied per model cycle rather than a one-off cost. In other words, the total subsequent treatment costs of patients progressing in the i^{th} cycle is a product of the 2L progression free survival (PFS) curve capped by mortality at the i^{th} cycle, cost of subsequent treatment per cycle (which differs by cycle), and the discount rates starting from the i^{th} cycle. The total subsequent treatment costs of patients progressing in the $i+1^{th}$ cycle is calculated similarly.

Tunnel states for tracking efficacy were deemed an unnecessary complexity given post-progression health states showed a constant rate of progression and death (i.e., the exponential distribution was a good fit to the RESONATE data in relapsed or refractory [R/R] CLL). At the request of the EAG, Janssen have provided Figure 7 in Appendix 3 of the separate appendix document which explains the detailed schematic diagram of the transitions in the model along with how costs and utilities are accrued. Appendix 4 outlines the approach employed to accrue subsequent treatment acquisition costs which involves the tracking of patient cohorts stratified by the cycle when they initiated subsequent treatment.

Clinical parameters and variables

B2. PRIORITY. Section B.3.3.1. For each of the patient populations included in the analysis, please provide a table comparing the key details of the trials and patient characteristics for each data source used. Please also comment on the comparability of the different clinical data sources used in the model and any bias introduced as a result of key differences.

FCR-suitable population

In the analysis provided to NICE/EAG, the main sources of data utilised in the economic model were the clinical trials (E1912 and CAPTIVATE FD cohort) and the ITC. The ITC of I+V vs. FCR in the FCR-suitable population used in the model compared data from the ECOG-1912 (E1912) trial and the FD cohort of the CAPTIVATE trial. IPD were available from both trials, therefore propensity score comparisons were used which adjusted for differences to generate the comparative efficacy estimates. Key trial details and patient characteristics are summarised in Table 4 below. Based on the trial eligibility criteria, the enrolled patients were comparable by:

- Diagnosed with CLL
- Treatment-naïve and required treatment per iwCLL 2008 criteria
- Aged between 18 and 70 years (both inclusive)
- Have an ECOG performance score (PS) 0-2

A key difference in inclusion/exclusion criteria was that E1912 excluded patients with del17p while the CAPTIVATE study FD cohort included 20 patients with del17p and three patients with unknown del17p or TP53 mutation status. Therefore, only patients with no del17p in the CAPTIVATE FD cohort were included in the ITC analysis.

In a comparison of the characteristics of the trial populations, patients in the CAPTIVATE FD cohort were slightly older (mean and median values) and had a higher proportion of patients aged over 65 years compared to the E1912 trial. Patients in the CAPTIVATE FD cohort also had slightly better ECOG PS and fewer instances of advanced disease (Rai stage 3/4) than those in the E1912 study. The

CAPTIVATE FD cohort appeared to have fewer patients with unmutated immunoglobulin heavy-chain variable gene region (IGHV); however, >20% of patients in E1912 had no reported IGHV testing results. TP53 mutational status was impacted by missing data in both studies, but more so in E1912, where a higher rate of missingness was recorded. Sensitivity analyses were performed to exclude patients with known TP53 mutation, and missing TP53 mutation information and it was concluded that the outcomes remained similar or slightly improved for I+V in these analyses. The CAPTIVATE study did not collect and report Cumulative Illness Rating Scale (CIRS) score data, while the E1912 study did not report on complex karyotype, so no conclusion can be made about these characteristics. Other relevant characteristics (including proportion of patients with bulky disease, proportion of patients with del11q and proportion of patients with small lymphocytic lymphoma [SLL]) had similar distributions in both studies (Table 4). The baseline characteristics for all treated patients without del17p in CAPTIVATE FD cohort remained generally similar to those observed in the ITT populations of the respective trials.

In addition to baseline characteristics, there were some differences in the timing and frequency of assessments and computer tomography (CT) imaging between the two trials, particularly in the first year. CT scanning was done more frequently in CAPTIVATE than E1912 up until approximately 29 months after which both studies required CT imaging annually, but assessments were done more frequently in E1912 after the first year (every 3 months versus 3 times per year during years 2 and 3 and every 6 months thereafter in the CAPTIVATE trial). The differences in imaging may have resulted in some difference in the timing of events being captured if there were no other physical symptoms of progression.

Most of the differences between E1912 and the CAPTIVATE FD cohort described above are clinically meaningful prognostic factors and treatment-effect modifiers (TEMs), e.g. del17p, age, ECOG PS, IGHV mutation status, TP53 mutation status. CAPTIVATE FD cohort having a slightly older population than E1912 would bias results against I+V; however, CAPTIVATE FD cohort having patients with better PS, fewer instances of Rai stage 3 or 4 and fewer instances of unmutated IGHV would bias results in favour of I+V. Therefore, it is likely the two would cancel each other out, although it is hard to predict the overall impact of the differences between the

E1912 and FD CAPTIVATE cohort outlined above, i.e., whether they would favour I+V or not.

Given that IPD was available for both trials, there was an extensive number of variables available to be matched. Janssen sought validation from clinical experts on variables to match on to improve the clinical validity. A naïve comparison would yield potentially biased estimates; therefore, in line with guidance from Decision Support Unit (DSU) Technical Support Document (TSD)18,(7) propensity score weighting was used for matching the two cohorts as the most robust method, given IPD was available from both trials.

Findings of the propensity score comparisons were generally consistent across scenarios and weighting approaches [i.e., either weighting to the CAPTIVATE or E1912 trials using average treatment effect in the treated population (ATT), average treatment effect in the control population (ATC) and average treatment effect in the combined/overall population (ATO), indicating the robustness of results. The hazard ratios (HRs) across weighting approaches and scenarios were tested in the economic model, and results were consistent with the base case results; I+V remains a cost-effective use of resources.

Overall, Janssen used the most robust method (propensity score weighting) to make the populations from E1912 and CAPTIVATE FD cohort most comparable given the availability of evidence. Although there are biases present, Janssen note these are unlikely to significantly impact the results.

Table 4 Key trial details and patient characteristics: FCR-suitable

	E1912	**CAPTIVATE FD cohort (non-del17p)**
Study design		
	Phase III, RCT	Phase II
Study population		
Patients, n	I+R: 354 FCR: 175	I+V: 136
Median age in years (range)	I+R: 58 (31–70) FCR: 57 (28-70)	I+V: 60 (33-71)
Male (%)	I+R: 66.7% FCR: 68.6%	I+V: 65%
ECOG PS 0/1/2 (%)	I+R: 63.8%/33.6%/2.5% FCR: 62.3%/36.0%/1.7%	I+V: 71%/29%/0%

	E1912	CAPTIVATE FD cohort (non-del17p)
del17p (%)	I+R: 0.6%* FCR: 0.0%*	Excluded
TP53 mutation (%)	I+R: [redacted] FCR: [redacted]	I+V: 5%
ulGHV (%)	I+R: 75.0%** FCR: 61.7%**	I+V: 57%
Rai stage 3-4 (%)	I+R: 44.1% FCR: 41.1%	I+V: 25%
Bulky disease ≥5 cm (%)	I+R: [redacted] FCR: [redacted]	I+V: 32%
del11q (%)	I+R: 22.2% FCR: 22.3%	I+V: 21%
Complex karyotype (%)	Not reported	I+V: 18%
CIRS >6 (%)	I+R: [redacted] FCR: [redacted]	Not reported
Median CIRS score	Not reported	Not reported
CrCl <60 mL/min (%)	I+R: [redacted] FCR: [redacted]	I+V: 4%
Median CrCl, mL/min	I+R: 94.8 FCR: [redacted]	I+V: 89.5
β2-M (>3.5 mg/L) (%)	I+R: [redacted] FCR: [redacted]	Not reported
SLL patients	I+R: [redacted] FCR: [redacted]	I+V: 8%
Median time from diagnosis	I+R: [redacted] FCR: [redacted]	I+V: 37.4 months
Eligibility criteria	• Previously untreated CLL or SLL requiring treatment per iwCLL criteria • Aged ≤70 years • CrCl >40 mL/min • Excluded patients with del17p	• Previously untreated CLL or SLL requiring treatment per iwCLL criteria • Aged ≥18 and ≤70 years • Measurable nodal disease by CT • ECOG PS of 0 to 2 • Adequate hepatic, renal, and hematologic function
Treatment		
Intervention	I+R: ibrutinib administered 420 mg per day until disease progression and rituximab was administered at 50 mg/m^2 on day 1 of cycle 2; 325 mg/m^2 on day 2 of cycle 2; and 500 mg/m^2 on day 1 of cycles 3-7.	I+V: 3 cycles of single-agent ibrutinib (420 mg once daily) followed by 12 cycles of combined ibrutinib plus venetoclax (target dose 400 mg once daily after standard 5-week ramp-up, with TLS prophylaxis and monitoring per US prescribing information). Treatment was administered in 28-day cycles.
Comparator	FCR: Six courses of intravenous fludarabine were administered at 25 mg/m^2 and cyclophosphamide was administered at 250 mg/m^2 on days 1-3, in combination with rituximab administered at 50 mg/m^2 on day 1 of cycle 1; 325 mg/m^2 on day 2 of cycle 1; and 500 mg/m^2 on day 1 of cycles 2–6 every 28-days.	N/A (single arm)

	E1912	CAPTIVATE FD cohort (non-del17p)
Outcomes		
Primary Endpoint	PFS	CR
Key secondary endpoints	OS, safety, HRQoL	PFS, OS, DOR, MRD, ORR, reduction in tumour burden category for TLS prophylaxis, safety

β2-M = Beta 2 microglobulin; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CR = complete response rate; CrCl = creatinine clearance; CT = computerised tomography; del11q = 11q deletion; del17p = 17p deletion; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; HRQoL = health-related quality of life; I+R = ibrutinib + rituximab; I+V = ibrutinib + venetoclax; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; SLL = small lymphocytic lymphoma; TLS = tumour lysis syndrome; TP53 = tumour protein 53; uIGHV = unmutated immunoglobulin heavy-chain variable gene region; US = United States

*inclusion of del17p patients was a protocol deviation (discovered after randomisation)

**of patients with a conclusive result for IGHV status. 21% in I+R and 34% in FCR were not tested or sample could not be sequenced.

***Total sample includes patients with missing CIRS score ([redacted] in I+R and [redacted] in FCR had missing results)

****Total sample includes patients with missing TP53 mutation testing result ([redacted] in I+R and [redacted] in FCR had missing test result)

Source: EMA, 2022 (Assessment Report);(1) Pharmacyclics LLC, 2019 (E1912 CSR);(8) Shanafelt, 2019 (NEJM)(9)

FCR-unsuitable and high-risk populations

In the analysis provided to NICE/EAG, the main sources of data utilised in the economic model for both the FCR-unsuitable and high-risk populations were anchored MAICs. These compared I+V vs. VenO (based on trial data from GLOW and CLL14) and I+V vs. acalabrutinib monotherapy (based on trial data from GLOW and ELEVATE-TN). Key trial details and patient characteristics are summarised in Table 5 and graphically in Figure 1.

Given all trials (GLOW, CLL14 and ELEVATE-TN) had obinutuzumab + chlorambucil (O-Clb) as a comparator arm, anchored forms of ITC (Bucher and anchored MAIC) were considered for methodological completeness. Given the differences in distribution of TEMs, anchored MAIC analyses were preferred over Bucher analyses since they aim to adjust for imbalances in TEMs and thus provide an unbiased estimate of treatment effect.

The MAIC methodology requires use of IPD from one of the trials and only aggregate data from the other trial. It accounts for cross-trial differences in patient baseline characteristics, which could otherwise bias the comparison between treatments. Patients in the GLOW trial who did not meet the inclusion/exclusion criteria of the comparator trial were removed and the remaining patients were reweighted with an

approach similar to propensity-score weighting (a tool widely used in observational research). After matching, treatment outcomes are compared across balanced trial populations.

With regards to the anchored MAIC of I+V vs. VenO, both trials included in the analysis (GLOW and CLL14) were randomised phase III studies in patients ineligible for fludarabine-based therapies using O-Clb as a comparator. Differences were observed between the two trials in inclusion/exclusion criteria:

- CLL14 included previously untreated adult CLL patients who had a considerable burden of comorbidity defined as CIRS score >6 or impaired renal function defined by creatinine clearance (CrCl) <70 mL/min regardless of age. GLOW inclusion criteria required only patients between the ages of 18 and 64 (inclusive) to have a CIRS score >6 or CrCl <70 mL/min to be eligible, while patients who were 65 years old or older were eligible regardless of their CIRS score.
- CLL14 allowed inclusion of patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-3 while only patients with ECOG PS 0-2 were included in GLOW study.
- CLL14 included patients with any cytogenetic profile, including patients with del17p and TP53 mutation. In GLOW, patients with del17p were excluded as were patients with TP53 mutation if they were known to harbour it at time of inclusion in study. GLOW did not require mandatory testing for TP53 mutation at inclusion; therefore, patients without a result of this test were included if they met the other criteria for eligibility. It was later known that some patients in GLOW harboured TP53 mutation (N=9), mostly in the I+V arm.

Differences in inclusion criterion of CIRS score and CrCl requirements were addressed by excluding patients in GLOW who did not meet this criterion. However, inclusion of patients with del17p and ECOG PS 3 in CLL14 could not be directly addressed as there were no patients with these characteristics in GLOW. The share of patients with ECOG PS 3 in CLL14 was extremely low [1 of 216 (0.5%) in the VenO group and 0 of 216 (0%) in the O-Clb group] and was thus not expected to impact the overall results. TP53 mutation and del17p are considered equal in terms

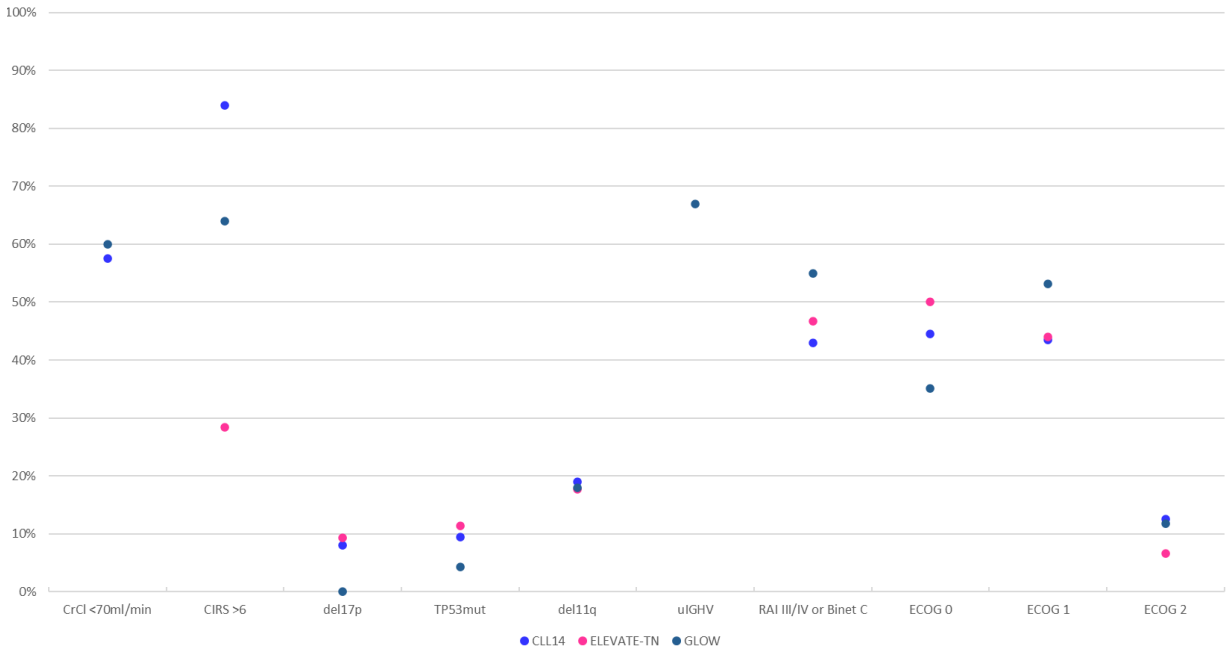
of treatment effect modification, therefore matching TP53 mutation could partially address the exclusion of del17p.

With regards to the anchored MAIC of I+V vs. acalabrutinib, both trials included in the analysis (GLOW and ELEVATE-TN) were randomised phase III studies in patients ineligible for fludarabine-based therapies using O-Clb as a comparator. No additional ELEVATE-TN trial exclusion criteria were applied for the GLOW population based on trial eligibility criteria. One key difference was identified in the trial design of GLOW and ELEVATE-TN; ELEVATE-TN allowed inclusion of patients with del17p and TP53 mutation. In GLOW, patients with del17p were excluded, as were patients with TP53 mutation if they were known to harbour it at the time of inclusion in the study. GLOW did not require mandatory testing for TP53 mutation at inclusion; therefore, patients without a result of this test were included if they met the other criteria for eligibility. It was later known that some patients in GLOW harboured TP53 mutation (N=9), mostly in the I+V arm. TP53 mutation and del17p are considered equal in terms of treatment effect modification, therefore matching TP53 mutation could partially address the exclusion of del17p.

The overlap of populations between GLOW and CLL14, or GLOW and ELEVATE-TN can be seen by the application of exclusion criteria and the reduction in the effective sample size within the MAICs (see Table 2 and Table 3). Even though no exclusion was necessary in the comparison versus ELEVATE-TN, there were notable differences between the populations recruited in the studies.

Janssen sought validation from clinical experts to ensure the approach was as robust as it could be methodologically and clinically. Clinical experts confirmed there were no missing TEMs which should be further adjusted for, and confirmed that age, ECOG PS, CIRS score and TP53 status should be the top-ranking characteristics to adjust in analyses without a compromising trade-off on sample sizes. Matching further characteristics would yield unreliable estimates, as they would be based on too small sample sizes.

Figure 1 Distribution (average of individual treatment arms in study) of characteristics* in CLL14, ELEVATE-TN and GLOW measured as share of included population



CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CrCl = creatinine clearance; del11q = 11q deletion; del17p =17p deletion; ECOG = European Cooperative Oncology Group; TP53mut = tumour protein 53 mutation; uIGHV = unmutated immunoglobulin heavy chain variable region
* Note that not all characteristics included in the MAICs are presented here. Characteristics such as age and those with median values cannot be expressed in the same scale.

There are other sources of potential bias which are not accounted for within the I+V vs. VenO MAIC which should be acknowledged for completeness and transparency. However, the impact on results is expected to be minimal:

It was not possible to match characteristic categories which were reported in CLL14, notably del17p; but since TP53mut was available and considered to be an equivalent predictor of poor prognosis, Janssen carried out an analysis in which TP53mut was matched for instead, hence minimising bias to the results. Additionally, dosing of chlorambucil in O-Clb differed between GLOW (maximum 6 cycles) and CLL14 (maximum 12 cycles). There are no head-to-head trials analysing the difference in outcomes due to differences in O-Clb dosing, however, published peer-reviewed NMAs suggest variation in chlorambucil dosing across various trials is not generally thought to impact results, evidenced by the inclusion of studies with these differences in networks (10-12) and use was accepted for the TA663. Therefore, the impact on results is expected to be minimal.

There are other sources of potential bias which are not accounted for within the I+V vs. acalabrutinib MAIC that should be acknowledged. However, the impact on results is expected to be minimal:

It was not possible to match del17p; but since TP53mut was available and considered to be an equivalent predictor of poor prognosis, Janssen carried out an analysis in which TP53mut was matched for instead, hence minimising bias to the results. Additionally, the ELEVATE-TN study did not report CIRS score for the entire population (with data missing for >30% of patients in each treatment group), and therefore this characteristic could not be matched.

Finally, as with any analysis, there could be unreported or unobserved confounding factors which could not be adjusted for. It was not possible to adjust for differences in outcome detection in either of the MAICs, as observed in assessments of PFS where a CT scan/magnetic resonance imaging (MRI) was required on most disease evaluation visits in GLOW regardless of suspicion of disease progression, while CT/MRI was only required when investigator had suspicion of disease progression in CLL14 and ELEVATE-TN. Considering that in anchored MAIC the relative effect within RCT is used, the impact of more rigorous use of imaging in detection of progression is not expected to impact outcomes as imaging would affect both treatment groups in the GLOW study and the relative effect would remain unchanged, therefore having a minimal impact on results.

Table 5 Key trial details and patient characteristics: FCR-unsuitable

	GLOW	CLL14	ELEVATE-TN*
Study design			
	Phase III, RCT	Phase III, RCT	Phase III, RCT
Study population			
Patients, n	I+V: 106 O-Clb: 105	VenO: 216 O-Clb: 216	Acalabrutinib + O: 179 Acalabrutinib: 179 O-Clb: 177
Median age in years (range)	I+V: 71.0 (47-93) O-Clb: 71.0 (57-88)	VenO: 72 (43–89) O-Clb: 71 (41–89)	Acalabrutinib + O: 70 (41–88) Acalabrutinib: 70 (44-87) O-Clb: 71 (46-91)
Male (%)	I+V: 55.7% O-Clb: 60.0%	VenO: 67.6% O-Clb: 66.2%	Acalabrutinib + O: 62% Acalabrutinib: 62% O-Clb: 60%
ECOG PS (%)	**PS 0/>0** I+V: 33/67 O-Clb: 37/63	**PS 0/>0** VenO: 41.2/ 58.8 O-Clb: 47.9/ 52.1	**PS ≤1/2** Acalabrutinib + O: 94.4/5.6 Acalabrutinib: 92.2/ 7.8 O-Clb: 94.4/ 5.6
del17p (%)	Excluded	VenO: 8.5 O-Clb: 7.3	Acalabrutinib + O: 9.5 Acalabrutinib: 8.9 O-Clb: 9.0

	GLOW	CLL14	ELEVATE-TN*
TP53 mutation (%)	I+V: 7% O-Clb: 2%	VenO: 11% O-Clb: 8%	Acalabrutinib + O: 12% Acalabrutinib: 11% O-Clb: 12%
uIGHV (%)	I+V: 51.9§ O-Clb: 51.4§	VenO: 60.5 O-Clb: 59.1	Acalabrutinib + O: 57.5 Acalabrutinib: 66.5 O-Clb: 65.5
Rai stage 3-4 (%)	I+V: 57% O-Clb: 53%	Not reported	Acalabrutinib + O: 47% Acalabrutinib: 49% O-Clb: 44%
Binet stage C (%)	I+V: 44.8% O-Clb: 39.6%	VenO: 43.1% O-Clb: 42.6%	Not reported
Bulky disease ≥5 cm (%)	I+V: 39% O-Clb: 36%	Not reported	Acalabrutinib + O: 26% Acalabrutinib: 38% O-Clb: 31%
del11q (%)	I+V: 19% O-Clb: 17%	VenO: 18% O-Clb: 20%	Acalabrutinib + O: 17% Acalabrutinib: 17% O-Clb: 19%
Complex karyotype (%)	Not reported	Not reported	Acalabrutinib + O: 16% Acalabrutinib: 17% O-Clb: 18%
CIRS >6 (%)	I+V: 70% O-Clb: 58%	VenO: 86% O-Clb: 82%	Not reported
Median CIRS score	I+V: 9 O-Clb: 8	VenO: 9 O-Clb: 8	Acalabrutinib + O: 6.0 (measured in 65% of patients) Acalabrutinib: 6.0 (measured in 64% of patients) O-Clb: 5.5 (measured in 67% of patients)
CrCl <60 mL/min (%)	Not reported	Not reported	Acalabrutinib + O: 25% Acalabrutinib: 27% O-Clb: 32%
CrCl <70 mL/min (%)	Not reported	VenO: 60% O-Clb: 55%	Not reported
Median CrCl, mL/min	I+V: 66.5 O-Clb: 63.2	VenO: 65.2 O-Clb: 67.5	Acalabrutinib + O: 76.5 Acalabrutinib: 75.0 O-Clb: 70.0
β2-M (>3.5 mg/L) (%)	I+V: 70% O-Clb: 73%	VenO: 59% O-Clb: 62%	Acalabrutinib + O: 74% Acalabrutinib: 78% O-Clb: 75%
Median time from diagnosis	I+V: 35.8 months O-Clb: 35.4 months	VenO: 31.2 months O-Clb: 29.2 months	Acalabrutinib + O: 30.5 months Acalabrutinib: 24.4 months O-Clb: 30.7 months
ANC ≤1,500 microL (%)	I+V: [redacted] O-Clb: [redacted]	Not reported	Acalabrutinib + O: 5% Acalabrutinib: 6% O-Clb: 3%
Haemoglobin ≤11g/dl (%)	I+V: [redacted] O-Clb: [redacted]	Not reported	Acalabrutinib + O: 37% Acalabrutinib: 38% O-Clb: 39%
Platelets ≤100,000 microL (%)	I+V: [redacted] O-Clb: [redacted]	Not reported	Acalabrutinib + O: 25% Acalabrutinib: 18% O-Clb: 19%
Cytopenia at baseline (%)	I+V: [redacted] O-Clb: [redacted]	Not reported	Acalabrutinib + O: 52% Acalabrutinib: 48% O-Clb: 44%
Region – Europe (%)	I+V: [redacted] O-Clb: [redacted]	Not reported	Acalabrutinib + O: 54% Acalabrutinib: 49% O-Clb: 52%
Eligibility criteria	• Previously untreated CLL/SLL requiring treatment per iwCLL criteria • Aged ≥65 years or 18–64 years	• Previously untreated CLL requiring treatment per iwCLL criteria • Aged ≥18 years • Coexisting conditions with a score of >6 on the CIRS score or CrCl <70 mL/min	• Previously untreated CLL requiring treatment per iwCLL criteria • Aged 65 years or older, or older than 18 years and younger than 65 years with comorbidities (CrCl of 30–69 mL/min calculated by

	GLOW	CLL14	ELEVATE-TN*
	with CIRS score >6 or CrCl<70 mL/min • ECOG PS score ≤2 • Excluded patients with del17p or known TP53 mutations	• Adequate marrow and liver function	use of the Cockcroft-Gault equation or CIRS score >6) • ECOG PS score ≤2 • Adequate hematologic, hepatic, and renal function • Excluded patients with significant cardiovascular disease
Treatment			
Intervention	I+V FD: 3 cycles of single-agent ibrutinib (420 mg once daily) followed by 12 cycles of combined ibrutinib plus venetoclax (target dose 400 mg once daily after standard 5-week ramp-up, with TLS prophylaxis and monitoring per US prescribing information). Treatment was administered in 28-day cycles.	VenO: the treatment duration consisted of 12 cycles lasting 28 days each. Daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1,000 mg on day 1), 1,000 mg on day 8 and 1,000 mg on day 15 of cycle 1, and subsequently 1,000 mg on day 1 of cycles 2 through 6.	Acalabrutinib + O: oral acalabrutinib was administered (100 mg) twice a day until progressive disease or unacceptable toxic effects occurred. Acalabrutinib was given for one cycle before obinutuzumab. Intravenous obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1,000 mg), and 15 (1,000 mg) of cycle 2 and on day 1 (1,000 mg) of cycles 3–7. Acalabrutinib: oral acalabrutinib was administered (100 mg) twice a day until progressive disease or unacceptable toxic effects occurred.
Comparator	O-Clb: obinutuzumab and chlorambucil were given for 6 cycles lasting 28 days each. Chlorambucil was administered orally at 0.5 mg per kg of body weight on days 1 and 15 of each cycle. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1,000 mg on day 1), 1,000 mg on day 8 and 1,000 mg on day 15 of cycle 1, and subsequently 1,000 mg on day 1 of cycles 2 through 6.	O-Clb: obinutuzumab and chlorambucil were given for 12 cycles lasting 28 days each. Chlorambucil was administered orally at 0.5 mg per kg of body weight on days 1 and 15 of each cycle. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1,000 mg on day 1), 1,000 mg on day 8 and 1,000 mg on day 15 of cycle 1, and subsequently 1,000 mg on day 1 of cycles 2 through 6.	O-Clb: obinutuzumab and chlorambucil were given for 6 cycles lasting 28 days each. Chlorambucil was administered orally at 0.5 mg per kg of body weight on days 1 and 15 of each cycle. Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2, 1,000 mg on day 8 and 1,000 mg on day 15 of cycle 1, and subsequently 1,000 mg on day 1 of cycles 2 through 6.
Outcomes			
Primary Endpoint	PFS	PFS	PFS
Key secondary Endpoints	OS, uMRD in bone marrow, ORR, CR, TTNT, HRQoL, hematologic improvement	OS, EFS, ORR, CR, PR, DOR, MRD negativity, time to new antileukemic treatment, HRQoL	OS, ORR, TTNT, safety, HRQoL

ANC = absolute neutrophil count; β2-M = Beta 2 microglobulin; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CR = complete response rate; CrCl = creatinine clearance; del11q = 11q deletion; del17p = 17p deletion; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; FCR = fludarabine + cyclophosphamide + rituximab; FD = fixed duration; HRQoL = health-related quality of life; I+V = ibrutinib + venetoclax; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; MRD = minimal residual disease; O-Clb = chlorambucil + obinutuzumab; O = obinutuzumab; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial

response; PS = performance status; RCT = randomised controlled trial; SLL = small lymphocytic lymphoma; TLS = tumour lysis syndrome; TP53 = tumour protein 53; TTNT = time to next treatment; uIGHV = unmutated immunoglobulin heavy-chain variable gene region; uMRD = undetectable minimal residual disease; US = United States; VenO = venetoclax + obinutuzumab

§ Total sample includes patients with missing result (23% missing in each arm)

Source: Fischer, 2019 (NEJM);(13) Kater, 2022 (NEJM);(14) Sharman, 2020 (Lancet);(15) Sharman, 2022 (Leukemia)(16)

Subsequent treatment

Economic model inputs related to subsequent treatment (including post-progression survival [PPS] and subsequent treatment duration) were informed by a subgroup of patients treated with a Bruton's tyrosine kinase inhibitor (BTKi; ibrutinib) in the RESONATE trial who had had 1 to 2 prior lines of therapy. Key trial details for this subgroup in the RESONATE ibrutinib arm are presented in Table 6. A larger proportion of patients were <70 years of age and there is a more substantial proportion of patients with del17p which is in line with observations that del17p can develop over time and is thus recommended to be tested for before starting every new line of CLL therapy for patients who previously tested negative for it.(17, 18) The age of some of the patients in RESONATE are younger than those in the GLOW trial, however, the RESONATE trial has other factors which capture poor prognosis such as del17p. In addition, the economic model adjusts for mortality events by using general population mortality ± standardised mortality ratio (SMR) to also account for age. Age in this subgroup of RESONATE is in line with other recent trials in similar settings such as MURANO (median age 64.5 and 66 years for each treatment group respectively)(19) and ASCEND (median age 67-68 years for each treatment group respectively).(20)

Data inputs for subsequent treatment in the model were informed by patients who have had 1-2 prior lines of therapy from RESONATE and are representative of CLL patients who have received 1L treatment and are now receiving 2L or 3L treatment. The generalisability of this cohort to the target population minimises bias.

Table 6 Key trial details and patient characteristics: 2L+

Trial	**RESONATE (1-2 prior lines subgroup) – used in the model**	
Study design		
	Subgroup of phase III, RCT	
Study population*		
Patients, n	1 or 2 prior lines population	92

Trial	RESONATE (1-2 prior lines subgroup) – used in the model	
Age	Median years, (min-max)	66.0 (30-86)
	<65 years, n (%)	39 (42.4)
	≥65 years, n (%)	53 (57.6)
	<70 years, n (%)	58 (63)
	≥70 years, n (%)	34 (37)
Gender	Female, n (%)	29 (31.5)
	Male, n (%)	63 (68.5)
ECOG PS	0, n (%)	41 (44.6)
	1, n (%)	51 (55.4)
CrCl	<60 mL/min, n (%)	24 (26.1)
β2-M	>3.5 mg/L, n (%)	67/85 (78.8)
IGHV status	Missing, n (%)	24 (26.1)
	Mutated, n (%)	10 (10.9)
	Unmutated, n (%)	58 (63)
Del17p status	No, n (%)	68 (73.9)
	Yes, n (%)	24 (26.1)
Del11q status	No, n (%)	63 (68.5)
	Yes, n (%)	29 (31.5)
	Not reported, n (%)	0
CIRS score	≥6, for ≥65 year olds only†, n (%)	35/52 (67.3)†
Rai stage	Stage 0, n (%)	2 (2.2)
	Stage I, n (%)	26 (28.3)
	Stage II, n (%)	16 (17.4)
	Stage III, n (%)	13 (14.1)
	Stage IV, n (%)	35 (38)
Bulky disease	<5 cm, n (%)	33 (35.9)
	≥5 cm, n (%)	59 (64.1)
	Missing, n (%)	0
Time from CLL diagnosis to randomisation	Median, months	66.07
Time from previous therapy	Median, months (min-max)	13.8 (1-94.9)
Resistant to purine analogues	n (%)	55 (59.8)
Region	Non-US, n (%)	47 (51.1)
	US, n (%)	45 (48.9)
	Australia, n (%)	8 (8.7)
	Europe, n (%)	39 (42.4)
	US, n (%)	45 (48.9)
Eligibility criteria	• CLL or SLL requiring treatment • Received at least 1 previous therapy • Inappropriate candidate for purine analog treatment because of a short progression-free interval after CIT or due to coexisting illnesses, age ≥70 years or presence of del17p • ECOG PS <2 • ANC of ≥750 cells/mL • Platelet count of ≥30,000 cells/mL • Adequate liver and kidney function • Excluded patients requiring warfarin or strong CYP3A4/5 inhibitor	

Trial	RESONATE (1-2 prior lines subgroup) – used in the model
Treatment	
Intervention	Ibrutinib administered orally 420 mg per day until disease progression or unacceptable toxicity

2L+ = second- and subsequent-line; β2-M = Beta 2 microglobulin; CIRS = Cumulative Illness Rating Scale; CIT = chemo-immunotherapy; CLL = chronic lymphocytic leukaemia; CrCl = creatinine clearance; CYP3A = Cytochrome P450, family 3, subfamily A; del11q = 11q deletion; del17p = 17p deletion; ECOG = Eastern Cooperative Oncology Group; IGHV = immunoglobulin heavy-chain variable gene region; PS = performance status; RCT = randomised controlled trial; SLL = small lymphocytic lymphoma; US = United States

* Baseline characteristics are presented for patients treated with ibrutinib. Characteristics are not presented from the ofatumumab treatment arm.

† Scores on this test were required only for patients 65 years of age or older, and coexisting illnesses were not included in the scoring.

Source: Byrd (2014);(21) Brown (2018);(22) O'Brien (2019)(23); Janssen Data on File

B3. PRIORITY. Section B.3.3.1, page 126. The submission indicates that the CAPTIVATE trial was not used to derive PFS estimates in the model [redacted] and because the pattern of PFS events observed was inconsistent with that of the GLOW trial. Other data sources have, however, been used in the model with similar numbers of patients at risk (e.g., GLOW trial, Figure 24 used in FCR-unsuitable population). Please explain this apparent inconsistency and clarify how data sources were selected for use in the economic model.

The FCR arm from the E1912 trial was used to derive PFS estimates for the FCR-suitable population in the economic model, since this was identified as the most appropriate source for several reasons:

1. the low number of PFS events in the I+V arm (n=23 of 136 in the FD non-del17p cohort) during the follow-up in CAPTIVATE
2. the quick drop in the numbers at risk in the tail end of the CAPTIVATE follow-up which is a result of a very fast enrolment
3. the availability of a data source with longer follow-up for the reference curve from the FCR trial (E1912).

In addition, this approach ensured that the PFS estimates used in the model demonstrated clinical and logical consistency across the populations, i.e., PFS in the FCR-suitable population being higher than PFS in the FCR-unsuitable/high-risk populations. PFS with I+V based on CAPTIVATE is expected to be higher than GLOW since the patients enrolled in CAPTIVATE were younger and fitter relative to the GLOW trial population.

The model was modified, based on this request from EAG, to explore a scenario in which the CAPTIVATE trial is used as the reference arm. For consistency with the GLOW trial population extrapolations (i.e., PFS for FCR-suitable was expected to be higher or the same as for a less fit, older population), the exponential extrapolation of I+V in CAPTIVATE was selected. A HR of [redacted] for I+V vs FCR was applied to estimate the PFS curve for FCR.

Figure 2 shows the PFS extrapolation of I+V and FCR in the base case (E1912 Weibull – FCR; I+V – HR of [redacted] (ATC) vs FCR) and the scenario analyses (CAPTIVATE Exponential – I+V; FCR – HR of [redacted] (ATT) vs I+V).

Figure 2 Comparison of I+V and FCR arms in the base case (FCR- Weibull from E1912; I+V – HR (ATC) vs FCR) and the scenario analyses (I+V – Exponential from CAPTIVATE; FCR – HR (ATT) vs I+V)

ATC = average treatment effect in the control population; ATO = average treatment effect in the combined/overall population; ATT = average treatment effect in the treated population; FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; HR = hazard ratio; I+V = ibrutinib + venetoclax

Table 7 shows the results of the scenario analysis. The ICER only minimally increases from £8,277 in the base case to £8,360 when I+V was independently extrapolated from CAPTIVATE and FCR was informed via a HR vs I+V.

Table 7 FCR-suitable: Scenario analyses with I+V PFS from CAPTIVATE as the reference curve

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
E1912 FCR (Weibull) as reference curve (base case)									
I+V	[redacted]	12.84	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.83	[redacted]	[redacted]	2.01	[redacted]	£8,277	[redacted]	[redacted]
CAPTIVATE I+V (exponential) as reference curve (scenario analysis)									
I+V	[redacted]	13.37	[redacted]	-	-	-	-	-	-
FCR	[redacted]	11.72	[redacted]	[redacted]	1.64	[redacted]	£8,360	[redacted]	[redacted]

FCR = fludarabine + rituximab + cyclophosphamide; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; PFS = progression-free survival; QALY = quality-adjusted life year; WTP = willingness to pay

B4. Section B.3.3.4, page 153. It is noted that clinical inputs for the high-risk population are assumed to be similar to the FCR-unsuitable population. However, the RESONATE-2 trial in FCR-unsuitable patients was considered not representative of the high-risk population due to this trial not including patients with del17p and only a small number of patients with TP53. Please explain this inconsistency.

In the economic model, the RESONATE-2 trial was not used as a source of inputs for the efficacy of ibrutinib monotherapy in high-risk patients because ELEVATE-TN was seen as a better proxy than RESONATE-2, in particular to reflect the BTKi efficacy in a high-risk population (del17p/TP53 mutation). This is because ELEVATE-TN has more high-risk patients (16 vs. 0 patients with del17p and 19 vs. 12 patients with TP53 mutation in the acalabrutinib arm of ELEVATE-TN vs. the ibrutinib arm of RESONATE-2, respectively).(24-26) Janssen recognise that the wording in the submission for the rationale of not using RESONATE-2 could have been clearer, but want to highlight that the more appropriate source for the high-risk subgroup is to utilise the ELEVATE-TN data.

Furthermore, the additional reason for using ELEVATE-TN is that acalabrutinib is already a comparator in the FCR-unsuitable population and its relative effect versus I+V was established using the anchored MAIC data from GLOW and ELEVATE-TN. An alternative approach would be to conduct a propensity score weighting analysis

between RESONATE-2 and GLOW, but the addition of another ITC using another data source would increase uncertainty.

Finally, no further analysis was required to establish the relative treatment effect for Ibrutinib and I+V since acalabrutinib and ibrutinib have been shown to have equivalent efficacy. A recent head-to-head open-label trial (ELEVATE-RR) indicated that acalabrutinib and ibrutinib have similar efficacy in R/R high-risk patients (PFS HR 1.00; 95% CI: 0.79-1.27).(27) Janssen also notes precedence from previous appraisals; the treatment effect determined in a patient population experiencing R/R CLL was transposed to 1L CLL high-risk patients in TA429 and TA689, with the agreement from the Committee.(28, 29) Furthermore, international ESMO guidelines recommend both treatments as equal options.

B5. PRIORITY. Section B.3.3.2, Table 29, page 130. The model comparison between I+V and FCR assumes that the HR derived from the IPTW indirect treatment comparison can be applied indefinitely over the time horizon of the model. Please provide:

a) Evidence to support the proportional hazard assumption over the observed duration of follow-up in the IPTW analysis;

Janssen have conducted and displayed below, the results of the Schoenfeld residuals test, which is commonly used to assess the assumption of proportional hazards (PH). Visual inspection of both naïve and adjusted Kaplan-Meier (KM) curves for the comparison do not suggest that there is a violation of PH. Furthermore, the Schoenfeld test for both naïve and adjusted KM curves (shown below in Figure 3, Figure 4, Figure 5, and Figure 6) indicate no evidence of violation of PH during the observed follow-up for the data regardless of weighting method applied to individual patient data from studies (p-values >0.05). Appendix 4 include the KM graphs.

Figure 3 Schoenfeld Residuals Plot - Unadjusted Comparison

INV = investigator; PFS = progression-free survival

Figure 4 Schoenfeld Residuals Plot - Adjusted Comparison (ATT)

ATT = average treatment effect in the treated population; INV = investigator; PFS = progression-free survival

Figure 5 Schoenfeld Residuals Plot - Adjusted Comparison (ATC)

ATC = average treatment effect in the control population; INV = investigator; PFS = progression-free survival

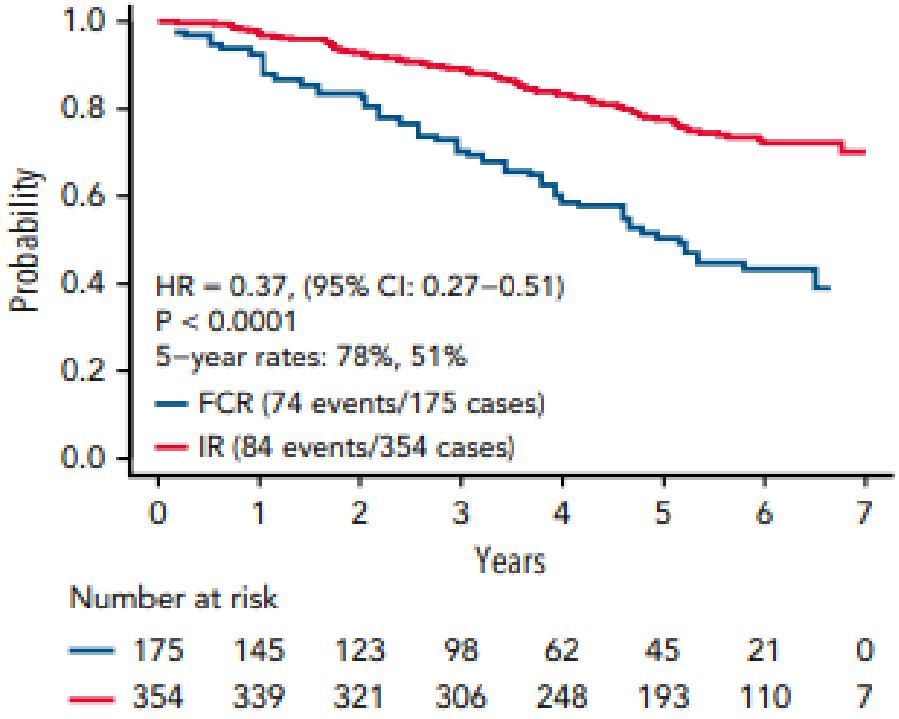
Figure 6 Schoenfeld Residuals Plot - Adjusted Comparison (ATO)

ATO = average treatment effect in the combined/overall population; INV = investigator; PFS = progression-free survival

b) Scenarios where the relative treatment effect of I+V versus FCR wanes over time.

Janssen have provided NICE/EAG with evidence of longer-term PFS data over a 7-year period effect (Figure 7). Based on this PFS data from the E1912 trial of an FCR-suitable population, which includes both FD FCR and treat to progression ibrutinib treatment, there are no noticeable large drops in the KM data with 5.8 years median follow-up in either arm which would indicate a loss of treatment effect (Figure 7).(30)

Figure 7 Long-term PFS data from E1912 trial (5.8 years median follow-up)



CI = confidence interval; FCR = fludarabine + cyclophosphamide + rituximab; IR = ibrutinib + rituximab; HR = hazard ratio; PFS = progression-free survival
Source: Shanafelt, 2022 (Blood)(30)

Due to a paucity of published data, Janssen sought feedback from clinical experts regarding the expectations of treatment waning over time. All clinicians (8) stated that this is very hard to predict and only 1 clinician stated that waning would most likely happen between 5 and 10 years. This would imply that this is an unlikely clinical scenario.

Therefore, at this request of the EAG, the economic model was modified to test treatment waning for the FCR-suitable population. In the base case, I+V is informed via an HR (0.46) vs FCR which is applied indefinitely over time. In the treatment waning scenario, it is assumed that the HR vs FCR increases in a linear fashion from 0.46 to 1 over the defined treatment waning period. In other words, I+V is equivalent to FCR by the end of the treatment waning period in this scenario.

In order to test the sensitivity of the model to treatment waning, multiple scenarios were run varying when waning starts (at 5 years and 10 years after stopping treatment with I+V) and the duration until equal benefit is achieved with I+V and FCR (i.e., HR=1). The results of the scenario analyses are presented in Table 8.

Given the feedback from clinical experts, in the most pessimistic scenario in which treatment waning starts at 5 years and over the subsequent 5 years achieves an HR of 1, the ICER remains under 30,000 per QALY. Overall, when testing this unlikely clinical scenario, it demonstrates that when accounting for scenarios where the relative treatment effect of I+V versus FCR wanes over time, I+V remains a cost-effective treatment option.

Table 8 Scenarios with Treatment Waning for FCR-suitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Base case – No treatment waning									
I+V	[redacted]	12.84	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.83	[redacted]	[redacted]	2.01	[redacted]	£8,277	[redacted]	[redacted]
Scenario 1: **Treatment waning start:** 5 years after treatment regimen stop **Duration to achieve equal benefit (i.e., HR of 1):** 10 years									
I+V	[redacted]	12.40	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.83	[redacted]	[redacted]	1.57	[redacted]	£23,903	[redacted]	[redacted]
Scenario 2: **Treatment waning start:** 5 years after treatment regimen **Duration to achieve equal benefit (i.e., HR of 1):** 5 years									
I+V	[redacted]	12.23	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.83	[redacted]	[redacted]	1.40	[redacted]	£29,634	[redacted]	[redacted]
Scenario 3: **Treatment waning start:** 10 years after treatment regimen **Duration to achieve equal benefit (i.e., HR of 1):** 10 years									
I+V	[redacted]	12.69	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.83	[redacted]	[redacted]	1.86	[redacted]	£16,109	[redacted]	[redacted]

FCR = fludarabine + rituximab + cyclophosphamide; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; WTP = willingness to pay

B6. PRIORITY. Section B.3.3.3, Figure 25, page 142. The figure shows that the extrapolated exponential PFS curve for I+V (in FCR-unsuitable) is overridden by general population mortality from approximately [redacted], when [redacted] of the cohort remain alive and progression free. With pre-progression mortality also set equal to GPM, this seems to imply that [redacted] of the FCR unsuitable cohort are cured with I+V (i.e., face zero further risk of progression and a mortality rate in line with age/sex matched general population). Please a) discuss the plausibility of this implicit

assumption, and b) explore methods that retain an ongoing risk of progression indefinitely over the time horizon of the model.

Plausibility of implicit assumption that [redacted] of the FCR unsuitable cohort are cured with I+V

During the acalabrutinib NICE submission (TA689)(31), a clinical expert indicated that functional cure (defined as PFS becoming similar to general population mortality hazards, such that patients do not experience any additional risk of progression or death due to CLL) was possible. During an advisory board conducted in March 2022 by Janssen, which included clinical experts from the UK, a clinical expert treating CLL patients indicated that patients not experiencing progression in 10 years may essentially be cured. (32)

Long-term PFS and OS data observed in frontline CLL from the RESONATE-2 trial also suggests high survival rates are possible with novel targeted therapies. The OS and PFS over the 8-year long-term follow-up from the RESONATE-2 trial shows high progression-free and survival rates after nearly 8 years (90 months) with more than half of patients alive and still progression-free and 78% of patients alive at 7 years (

Figure 8). Of note, RESONATE-2 included patients who were older than those who in GLOW, CLL14 and ELEVATE-TN studies (only patients aged 65 or more were allowed to enrol in RESONATE-2), therefore it is plausible to expect even higher PFS and OS rates from GLOW, CLL14 and ELEVATE-TN.

Figure 8 Observed OS and PFS in the ibrutinib arm in RESONATE-2 (8 year follow up)

OS = overall survival; PFS = progression-free survival

Exploring methods which retain an ongoing risk of progression indefinitely over the time horizon of the model

At this request of the EAG, Janssen conducted additional scenarios to explore the impact of a lower percentage of patients being progression-free in the longer term compared to the base case analysis. This was achieved by applying a SMR to increase the number of death events in PFS. An SMR of 1.19 (the upper range of SMR from the VenO NICE submission [TA663]) was applied for analysis.(33) An SMR of 2 was also tested to determine the impact of earlier events. Figure 9 shows the PFS extrapolations of treatments in the FCR-unsuitable population and the corresponding curves capped by general population mortality (GPM) (dotted curves) and capped by elevated mortality using a SMR of 1.19 (hyphenated curves).

Figure 9 PFS extrapolations of treatments in the FCR-unsuitable population capped by the elevated mortality (SMR = 1.19) and the general population mortality

FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; PFS = progression-free survival; SMR = standardised mortality ratio; VenO = venetoclax + obinutuzumab

Table 9 displays the results of the scenario analysis when a SMR of 1.19 was used to capture the elevated mortality CLL patients experience. Table 9 shows that the proportion of patients who were treated with I+V and were alive and progression-free at 15 years decreases from [redacted] in the base case to [redacted] when a SMR of 1.19 is used to capture the increased risk of mortality in CLL. When a SMR of 2.0 was used, [redacted] of patients who were treated with I+V are alive and progression-free at the 15-year mark. Overall, the results across the scenarios are consistent with base case results; I+V remains a cost-effective use of resources.

Table 9 Scenario analysis with a SMR of 1.19 in the FCR-unsuitable population

Technologies	% of patients alive and PF at 15 years	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
		Costs	Lys	QALYs	Costs	LYs	QALYs			
Base case										
I+V	[redacted]	[redacted]	9.88	[redacted]				-		
O-Clb	[redacted]	[redacted]	8.14	[redacted]	[redacted]	1.74	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,546,602)	[redacted]	[redacted]
Scenario 1: SMR 1.19 to capture the elevated mortality										
I+V	[redacted]	[redacted]	9.50	[redacted]				-		
O-Clb	[redacted]	[redacted]	8.00	[redacted]	[redacted]	1.50	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	[redacted]	9.20	[redacted]	[redacted]	0.30	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	9.90	[redacted]	[redacted]	-0.41	[redacted]	less costly, less effective (£1,618,337)	[redacted]	[redacted]
Scenario 2: SMR 2.0 to capture the elevated mortality										
I+V	[redacted]	[redacted]	8.2	[redacted]				-		
O-Clb	[redacted]	[redacted]	7.4	[redacted]	[redacted]	0.8	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	[redacted]	8.1	[redacted]	[redacted]	0.1	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	8.5	[redacted]	[redacted]	-0.3	[redacted]	less costly, less effective (£2,050,867)	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; SMR = standardised mortality ratio; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

B7. Section B.3.3.3, Figure 27, pages 146-147. The seven-knot spline model is described and presented as the best fitting curve for O-Clb PFS. Please provide a figure comparing the alternative curves fits.

In Janssen's original submission, standard parametric functions were fitted to O-Clb PFS and were presented in Appendix O of Submission Form B. Based on the parametric functions tested, the 7-knot spline and the Weibull distribution fit the observed data well and concurrently provided clinically reasonable extrapolations. These were included in the base case and as a scenario analysis in the submission, respectively. Figure 10 presents the 7-knot spline versus the other standard parametric fits for O-Clb and Figure 11 presents the spline models.

From visual inspection of the observed data (Figure 10), there is a marked drop in the PFS of the O-Clb arm at around 15 months. This sharp drop can be attributed to PFS events that perhaps occurred earlier but were only captured at the protocol-specified mandatory imaging timepoints. There is a window of time (between 9 and 15 months) when imaging was not mandatory which likely resulted in a high number of progression events captured at 15 months. Since the standard parametric distributions did not capture the underlying hazards of O-Clb PFS, flexible parametric survival analyses (spline modelling) were conducted and considered to be the base case for O-Clb PFS extrapolations. Flexible parametric survival analyses allowed increased complexity to capture the irregular hazard shape due to the steep drop observed at around 15 months (Figure 10).

Overall, Janssen note that out of all the parametric fits, the 7-knot spline model was the most appropriate clinically and statistically since it fit the observed data well and produces long-term estimates which align with clinical opinion from the advisory board of clinical and health economic experts conducted in March 2022.

Figure 10 Standard parametric fits, 7-knot spline and observed O-Clb PFS

KM = Kaplan-Meier; O-Clb = obinutuzumab + chlorambucil; PFS = progression-free survival

Figure 11 Spline models and observed O-Clb PFS

O-Clb = obinutuzumab + chlorambucil; PFS = progression-free survival

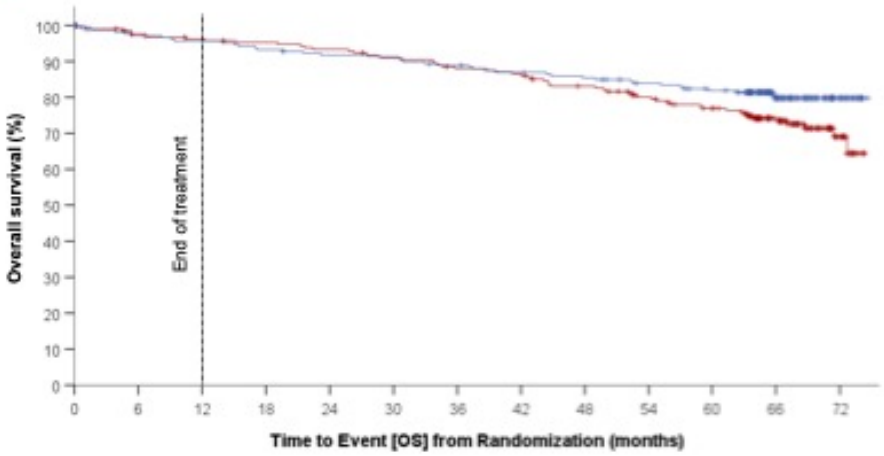
B8. Section B.3.3.3, page 152. It is noted that head-to-head data for acalabrutinib and VenO versus O-Clb in the respective CLL14 and ELEVATE-TN trials have shown overall similar OS. However, the model projects divergence in OS in favour of acalabrutinib and VenO versus O-Clb [redacted] (Figure 46). Please comment on the validity of the model OS projections against the latest available follow-up data from the CLL14 and ELEVATE-TN trials.

The 5-year follow-up from the CLL14 trial illustrates separation between VenO and O-Clb OS (Figure 12). A similar separation is shown in the model projections which is therefore credible and aligns to the trial data.

The ELEVATE-TN study currently does not have reliable estimates for 5-year OS published (where median follow-up exceeds 60 months) and therefore it is not possible to comment OS outcomes with certainty. The estimates are deemed uncertain because about half of the patients are censored at the 60-month point. Janssen has sought feedback from a clinical expert and they would expect OS would diverge in favour of acalabrutinib versus O-Clb by five years, similar to the trend observed in CLL14.

[redacted]. All the above evidence suggests that OS divergence in favour of VenO and acalabrutinib over O-Clb has face validity.

Figure 12 Observed OS in 5-year CLL14 data



Patients at risk													
Ven-Obi	216	201	198	193	189	188	182	177	173	166	159	97	25
Clb-Obi	216	206	201	198	194	188	181	177	167	155	144	101	21

Clb-Obi = obinutuzumab + chlorambucil; OS = overall survival; Ven-Obi = venetoclax + obinutuzumab

Source: Al-Sawaf, 2022 (EHA)(34)

Figure 13 Observed OS in [redacted] GLOW data

Clb+Ob = chlorambucil + obinutuzumab; Ibr+Ven = ibrutinib + venetoclax; OS = overall survival

Measurement and valuation of health effects

B9. Section B.3.4.5, Table 52. The PF utility value in the FCR-suitable population is higher than the general population value from HSE 2014. Please comment further on the face validity of this value that assumes patients with untreated CLL have a better quality of life than the general population without CLL.

Three large and independent trials, GLOW, CLL14 and ELEVATE-TN from different sponsors have all yielded EQ-5D scores which are higher than general population utility. This may be due to several reasons:

- The EQ-5D might not capture all aspects of the health-related quality of life (HRQoL) burden associated with CLL such as fatigue and disutility associated with IV treatment administration.(35) In contrast, EQ-5D may be more

sensitive to other ailments which impact HRQoL (e.g., depression, pain) which are prevalent in the general population.

- Patient-reported outcomes in general are reliant on patients' relative assessment of their wellbeing. Individuals from the general population would be expected to have roughly the same quality of life from day to day; however, a CLL patient who previously suffered from severe fatigue and started treatment which alleviated the fatigue and provided relief from symptoms would report a much higher quality of life the next day. Therefore, it is plausible that patients may report a progression-free utility which is higher than their general population counterparts. This thinking has been validated by clinical expert opinion.
- Patients included in the GLOW trial appropriately represented the population of CLL patients who are unsuitable for fludarabine-based CIT but are likely to tolerate less-intense treatment with O-Clb, based on age (≥65 years) or CIRS score >6 and CrCl <70 mL/min. The median patient age in GLOW was 71.0 years, which is similar to the median age of CLL diagnosis reported in England (72 years).(14, 36) Therefore, the HRQoL of patients from GLOW would accurately represent the target population who would likely be treated in clinical practice and should therefore be representative of the HRQoL of that cohort.

The fact that 3 trials which enrolled patients at different timepoints (CLL in 2014, ELEVATE-TN in 2015 and GLOW in 2018) and have different designs all while being carried out by different sponsors/trialists but have yielded similar utility values, implies that the utility values themselves are not a result of selection bias. The utility values from these 3 separate trials result in a strong evidence base, which needs to be acknowledged and factored into decision making.

Overall, scenarios in which utility values based on the age and gender adjusted general population values were tested in scenario analyses to explore the impact of alternative utility values (see response to clarification B10). The ICER of I+V versus FCR in the FCR-suitable population increased compared with the base case but remained under the £20,000 per QALY threshold. In the FCR-unsuitable and high-risk populations, the total QALYs and incremental QALYs gained by I+V decreased

slightly, but overall, the ICER findings did not change from the base case results; I+V remains a cost-effective use of resources.

B10. PRIORITY. Section B.3.4.5, Table 52. Please provide a sensitivity analysis which caps utility values in the model at age-adjusted population norms.

At the request of the EAG, Janssen have carried out a scenario analysis in which age-adjusted population utility norms are explored. However, Janssen note that this is a highly conservative scenario based on the evidence base and rationale provided in the response to B9. Table 10 provides the values used in the base case (which uses the PF 1L utility from the GLOW trial that is higher than the corresponding general population utility) and the scenario analyses (in which utility is capped by general population utility).

The general population utility for the FCR-suitable population was 0.849 (age = 58; male = 67.3%) and 0.798 for the FCR-unsuitable and high-risk populations (age = 71; male = 57.8%).(37) For the PF 2L and the PPS health states, the utility was derived from Holzner et al (38) which reported a utility of 0.6 (age = 68 for the cohort on which the value is based) and is consistent with the value used in TA689 and TA663 for post-progression state.

Table 10 Pre-progression (PF 1L) utility from GLOW vs. age-adjusted general population utility

Health condition	Estimate	Source
Base case		
FCR-unsuitable PF 1L	[redacted]	Utility derived from GLOW and adjusted for age and gender of CAPTIVATE
FCR-unsuitable/High-risk	[redacted]	Utility derived from GLOW
Scenario analysis: age and gender utility capped by general population utility		
FCR-suitable population (age = 58; male = 67.3%)	0.849	Hernández Alava (2022)(37)
FCR-unsuitable/high-risk population (age = 71; male = 57.8%)	0.798	

1L = first line; CI = confidence interval; FCR = fludarabine + cyclophosphamide + rituximab; HSE = Health Survey for England; NA = not applicable; PF = progression-free; UK = United Kingdom

Table 11, Table 12, and Table 13 present the scenario analysis in which the PF 1L utility was capped by the general population utility. The ICER of I+V versus FCR in the FCR-suitable population increased compared with the base case but remained

under the £20,000 per QALY threshold. In the FCR-unsuitable and high-risk populations, the total QALYs and incremental QALYs gained by I+V, decreased slightly, but overall, the ICER findings did not change from the base case analysis.

Even though this scenario is not likely clinically plausible, and is highly conservative, it demonstrates that even in the scenario, I+V is a cost-effective use of resources and is within the £20,000 WTP QALY threshold.

Table 11 FCR-suitable: Scenario Results capping by general population utility

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	12.69	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.83	[redacted]	[redacted]	[redacted]	[redacted]	£16,426	[redacted]	[redacted]

FCR = fludarabine + rituximab + cyclophosphamide; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; WTP = willingness to pay

Table 12 FCR-unsuitable: Scenario Results capping by general population utility

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.88	[redacted]	-	-	-	-	-	-
O-Clb	[redacted]	8.14	[redacted]	[redacted]	1.74	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,553,062)	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

Table 13 High-risk: Scenario Results capping by general population utility

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.88	[redacted]	-	-	-	-	-	-
Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£678,639)	[redacted]	[redacted]
VenO	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,553,062)	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

B11.Section B.3.4.5, Tables 52 and 53. The use of the same utility value for PF L2 and Post 2L progression lacks plausibility given the more than 10-fold difference in mortality rate between these states. Please explore scenarios where the post-progression utility value derived from the GLOW trial data is used for PF L2.

In the base case analysis, a utility for the PPS health state was derived from Holzner et al (38) which reported a utility of 0.6 (age = 68) for 2L and all other post-progression states by applying age adjustment. This approach was previously used in TA689 and TA663 where only a single utility value (0.60) was applied for the entire 'progressed disease' state, and accepted by the Committee.(29, 39)

Scenario analyses were performed in which alternative values for the post-progression states were evaluated. The value derived from GLOW of [redacted] (Table 46) was applied to PF 2L in one scenario, and also to PPS after 2L PFS in a second scenario. Table 14 summarises the utility stratified by health states by population.

Table 14 Starting utility by health states used in the economic model

Health state	FCR-suitable	FCR-unsuitable	High-risk	Source
Base case				
PF 1L	[redacted]	[redacted]	[redacted]	PF utility from GLOW
PF 2L	0.63†	0.59†	0.59†	Holzner et al (38)
PPS	0.63†	0.59†	0.59†	
Scenario 1: Use post-progression utility from GLOW to inform PF 2L				
PF 1L	[redacted]	[redacted]	[redacted]	PF utility from GLOW
PF 2L	[redacted]	[redacted]	[redacted]	PD utility from GLOW
PPS	0.63†	0.59†	0.59†	Holzner et al (38)
Scenario 2: Use post-progression utility from GLOW to inform PF 2L and PPS				
PF 1L	[redacted]	[redacted]	[redacted]	PF utility from GLOW
PF 2L	[redacted]	[redacted]	[redacted]	PD utility from GLOW
PPS	[redacted]	[redacted]	[redacted]	PD utility from GLOW

1L = first-line; 2L = second-line; FCR = fludarabine + cyclophosphamide + rituximab; PD = progressive disease; PF = progression-free; PPS = post-progression survival
† Utility derived from GLOW (measured age = 71) was adjusted to the FCR-suitable population whose starting age is 58. † Utility derived from Holzner et al (38) (measured age = 68) was adjusted to the FCR-suitable population and FCR-unsuitable/high-risk population whose starting ages are 58 and 71 respectively.

Table 15, Table 16, and Table 17 describe the scenario analyses results for the FCR-suitable, FCR-unsuitable, and high-risk populations, respectively. The conclusion of the scenario analyses is unchanged from the base case of the

submission, i.e. I+V is cost-effective vs FCR in the FCR-suitable population, I+V is dominant vs VenO and O-Clb and less costly, less effective vs acalabrutinib in the FCR-unsuitable population and I+V is dominant vs VenO and less costly, less effective vs acalabrutinib and ibrutinib in the high-risk population.

Table 15 Scenario using progressed disease utility from GLOW: FCR-suitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Scenario 1: Use post-progression utility from GLOW to inform PF 2L									
I+V	[redacted]	12.8	[redacted]	-	-	-	-	-	-
FCR	[redacted]	10.8	[redacted]	[redacted]	2.0	[redacted]	£9,547	[redacted]	[redacted]
Scenario 2: Use post-progression utility from GLOW to inform PF 2L and PPS									
I+V	[redacted]	12.8	[redacted]						
FCR	[redacted]	10.8	[redacted]	[redacted]	2.0	[redacted]	£9,739	[redacted]	[redacted]

2L = second-line; FCR = fludarabine + rituximab + cyclophosphamide; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; PF = progression-free; PPS = post-progression survival; QALY = quality-adjusted life year; WTP = willingness to pay

Table 16 Scenario using progressed disease utility from GLOW: FCR-unsuitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Scenario 1: Use post-progression utility from GLOW to inform PF 2L									
I+V	[redacted]	9.9	[redacted]	-	-	-	-	-	-
O-Clb	[redacted]	8.1	[redacted]	[redacted]	1.7	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.5	[redacted]	[redacted]	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.3	[redacted]	[redacted]	-0.4	[redacted]	less costly, less effective (£1,263,117)	[redacted]	[redacted]
Scenario 2: Use post-progression utility from GLOW to inform PF 2L and PPS									
I+V	[redacted]	9.9	[redacted]	-	-	-	-	-	-
O-Clb	[redacted]	8.1	[redacted]	[redacted]	1.7	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.5	[redacted]	[redacted]	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.3	[redacted]	[redacted]	-0.4	[redacted]	less costly, less effective (£1,240,565)	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; PF = progression-free; PPS = post-progression survival; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

Table 17 Scenario using progressed disease utility from GLOW: High-risk population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Scenario 1: Use post-progression utility from GLOW to inform PF 2L									
I+V	[redacted]	9.9	[redacted]	-	-	-	-	-	-
Ibrutinib	[redacted]	10.3	[redacted]	[redacted]	-0.4	[redacted]	less costly, less effective (£675,793)	[redacted]	[redacted]
VenO	[redacted]	9.5	[redacted]	[redacted]	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.3	[redacted]	[redacted]	-0.4	[redacted]	less costly, less effective (£1,546,602)	[redacted]	[redacted]
Scenario 2: Use post-progression utility from GLOW to inform PF 2L and PPS									
I+V	[redacted]	9.9	[redacted]				-		
Ibrutinib	[redacted]	10.3	[redacted]	[redacted]	-0.4	[redacted]	less costly, less effective (£541,224)	[redacted]	[redacted]
VenO	[redacted]	9.5	[redacted]	[redacted]	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.3	[redacted]	[redacted]	-0.4	[redacted]	less costly, less effective (£1,240,565)	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; PF = progression-free; PPS = post-progression survival; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

Cost and healthcare resource use identification, measurement and valuation

B12. Section B.3.5.1, Table 60, and section B.3.3.1 Please clarify whether the efficacy of treatments used in PF 2L is assumed to be equal in all patient populations, regardless of the treatment received, and estimated based on the ibrutinib arm of the RESONATE trial. If so, please comment further on the appropriateness of this assumption given only a minority of patients ([redacted] depending on first-line treatment) receive ibrutinib monotherapy in PF 2L.

Yes, the efficacy of treatments used in PF 2L is assumed to be equal in all patient populations, regardless of the treatment received, and estimated based on the ibrutinib arm of the RESONATE trial.

The ibrutinib arm of the RESONATE trial for patients who have received 1-2 prior lines subgroup is used because:

1. it reflects the efficacy of a BTKi
2. acalabrutinib and ibrutinib are assumed to have similar efficacy as validated by clinicians and detailed in clinical practice (ESMO) guidelines where both treatments are presented as equivalent options, and also accepted by the Committee in TA689.

Table 18 presents the use of BTKi compared to venetoclax + rituximab (VenR) in the subsequent treatment setting. The use of BTKi in the FCR-suitable population is similar for I+V and FCR (55% vs 56%). In the FCR-unsuitable population, the use of BTKi in the subsequent treatment setting is >60% for the FD treatments and 4% for acalabrutinib or ibrutinib. This trend is expected if patients are treated with BTKis at 1L that clinicians would initiate a treatment with a different mode of action after progression.(17, 18)

However, given that the majority of patients across the 3 populations receive mostly BTKi in the subsequent treatment setting, it is appropriate to model efficacy based on the ibrutinib arm of the RESONATE trial.

Table 18 Summary of subsequent treatment by drug category

Population	First-line treatment	Subsequent treatment	
		BTKi monotherapy	VenR
FCR-suitable population	I+V	[redacted]	[redacted]
	FCR	[redacted]	[redacted]
FCR-unsuitable and high-risk populations	I+V	[redacted]	[redacted]
	O-Clb†	[redacted]	[redacted]
	VenO	[redacted]	[redacted]
	Acalabrutinib	[redacted]	[redacted]
	Ibrutinib monotherapy†	[redacted]	[redacted]

FCR = fludarabine, cyclophosphamide, rituximab; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab
† Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population

B13. PRIORITY. Section B.3.5.1, Table 60. In the FCR-suitable population the proportions receiving subsequent treatments is similar in each arm of the model and, therefore, an assumption of equal efficacy may be reasonable. However, regarding the FCR-unsuitable/high-risk groups, this assumption may introduce bias in the model where the subsequent treatments differ (for example following acalabrutinib [redacted] of patients receive VenR but following I+V only [redacted] of patients receive this treatment). Please explain what bias this assumption may introduce in the model.

It is not plausible to assume that the proportions receiving subsequent treatments is similar in each arm of the model for the FCR-unsuitable/high-risk groups because of the following:

- only targeted agents are expected to be used in subsequent treatments in England
- ibrutinib and acalabrutinib are both in the class of BTKis which are administered until progression or unacceptable toxicity and are expected to have similar efficacy
- the clinical equivalence of ibrutinib continuous use and acalabrutinib in the R/R CLL setting was accepted in the NICE TA689 appraisal (29)
- establishing relative effect between VenR and continuous BTKi therapy has been problematic as highlighted by the NICE appraisal of VenR (TA561).(40) Further information about this is provided below.

- assuming the same clinical equivalence across subsequent treatments was an assumption used and accepted in prior NICE appraisals (TA663 and TA689).(29, 39)

In TA561 plausible ICERs for VenR and Ibrutinib monotherapy could not be determined due to neither MAIC nor network meta-analysis (NMA) being seen as fully appropriate or reliable methods to determine the relative effect mainly due to poor overlap between the populations of MURANO and RESONATE trials.(40) TA689 did not compare acalabrutinib to VenR for previously treated CLL patients and it was noted that it remains unclear if robust evidence to allow comparison for VenR versus acalabrutinib exists.(40)

When comparing reported PFS rates over time in studies with targeted agents in R/R CLL, it appears that FD VenR has lower long-term PFS rates than continuous ibrutinib (5-year PFS 37.8% vs 60% in 1-2 prior lines of ibrutinib from RESONATE and 52.7% in ibrutinib group from HELIOS; acalabrutinib 5-year data from ASCEND not yet reported), however a naïve comparison between both could also be biased. Considering that ibrutinib 1-2 prior lines offers the highest observed long-term PFS rates, the assumption of equivalent efficacy among targeted agents in post-progression state is likely conservative to ibrutinib. The assumption also reduces the impact of subsequent treatment on outcomes where subsequent targeted agent use is expected to differ for 1L treatments like in the FCR-unsuitable patient group.

In order to test the bias of this assumption, two scenarios were run to vary the efficacy of VenR vs the reference ibrutinib arm from RESONATE: 1) Assumed a VenR HR of 0.5 vs ibrutinib which is extremely conservative given that in TA561 a PFS HR 0.797 was seen as an underestimate of ibrutinib's efficacy by ERG; 2) Assumed a VenR HR of 1.5 vs ibrutinib which is close to the initial outcome of ERG's NMA in TA561 (PFS HR 1.43).(40)

Table 19, Table 20, and Table 21 present the scenario results for the FCR-suitable, FCR-unsuitable, and high-risk populations respectively. The conclusion of the scenario analyses is unchanged from the base case of the submission, i.e. I+V is cost-effective vs FCR in the FCR-suitable population, I+V is dominant vs VenO and O-Clb and less costly, less effective vs acalabrutinib in the FCR-unsuitable

population and I+V is dominant vs VenO and less costly, less effective vs acalabrutinib and ibrutinib in the high-risk population.

Table 19 Scenario using alternative subsequent treatment efficacy assumptions: FCR-suitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Base case (VenR = HR of 1)									
I+V	[redacted]	12.8	[redacted]						
FCR	[redacted]	10.8	[redacted]	[redacted]	2.0	[redacted]	£8,277	[redacted]	[redacted]
VenR = HR of 0.50									
I+V	[redacted]	12.2	[redacted]						
FCR	[redacted]	10.0	[redacted]	[redacted]	2.3	[redacted]	£12,272	[redacted]	[redacted]
VenR = HR of 1.50									
I+V	[redacted]	13.2	[redacted]						
FCR	[redacted]	11.4	[redacted]	[redacted]	1.8	[redacted]	£5,331	[redacted]	[redacted]

FCR = fludarabine + rituximab + cyclophosphamide; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenR = venetoclax + rituximab; WTP = willingness to pay

Table 20 Scenario using alternative subsequent treatment efficacy assumptions: FCR-unsuitable population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Base case (VenR = HR of 1)									
I+V	[redacted]	9.9	[redacted]						
O-Clb	[redacted]	8.1	[redacted]	-£86,281	1.7	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.5	[redacted]	-£91,913	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.3	[redacted]	-£414,388	-0.4	[redacted]	less costly, less effective (£1,546,602)	[redacted]	[redacted]
VenR = HR of 0.50									
I+V	[redacted]	9.7	[redacted]				-		
O-Clb	[redacted]	7.3	[redacted]	-£58,928	2.3	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.3	[redacted]	-£88,444	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	9.7	[redacted]	-£415,466	0.0	[redacted]	less costly, less effective (£9,761,867)	[redacted]	[redacted]
VenR = HR of 1.50									
I+V	[redacted]	10.0	[redacted]						
O-Clb	[redacted]	8.6	[redacted]	-£102,669	1.4	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.6	[redacted]	-£93,895	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.7	[redacted]	-£412,499	-0.7	[redacted]	less costly, less effective (£1,035,443)	[redacted]	[redacted]

HR = hazard ratio; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab; WTP = willingness to pay

Table 21 Scenario using alternative subsequent treatment efficacy assumptions: high-risk population

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Base case (VenR = HR of 1)									
I+V	[redacted]	9.9	[redacted]				-		
Ibrutinib	[redacted]	10.3	[redacted]	-£179,650	-0.4	[redacted]	less costly, less effective (£675,793)	[redacted]	[redacted]
VenO	[redacted]	9.5	[redacted]	-£91,913	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.3	[redacted]	-£414,388	-0.4	[redacted]	less costly, less effective (£1,546,602)	[redacted]	[redacted]
VenR = HR of 0.50									
I+V	[redacted]	9.7	[redacted]				-	[redacted]	[redacted]
Ibrutinib	[redacted]	9.7	[redacted]	-£179,894	0.0	[redacted]	less costly, less effective (£4,446,085)	[redacted]	[redacted]
VenO	[redacted]	9.3	[redacted]	-£88,444	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	9.7	[redacted]	-£415,466	0.0	[redacted]	less costly, less effective (£9,761,867)	[redacted]	[redacted]
VenR = HR of 1.50									
I+V	[redacted]	10.0	[redacted]			[redacted]	-	[redacted]	[redacted]
Ibrutinib	[redacted]	10.7	[redacted]	-£178,311	-0.7	[redacted]	less costly, less effective (£449,963)	[redacted]	[redacted]
VenO	[redacted]	9.6	[redacted]	-£93,895	0.4	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.7	[redacted]	-£412,499	-0.7	[redacted]	less costly, less effective (£1,035,443)	[redacted]	[redacted]

HR = hazard ratio; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab; WTP = willingness to pay

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care, Lymphoma Action and CLL Support Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** Leukaemia Care is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf. **Lymphoma Action** Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone.

	Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma. **CLL Support Association** CLL Support is the only UK CLL specific support charity which was formed in 2005 and is run entirely by volunteers. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLLSA provides support to the UK CLL community and CLLSA membership of 2,000+ association members who live with CLL or are carers and the 15,000+ CLLSA on-line community members on the Health Unlocked CLL Support platform (not all UK based). CLLSA provides up to 6 patient conferences a year including a regular Scottish patient's conference. Since 2020 the meeting have been via Webinars because of COVID19 and have been topical and more frequent. CLLSA support patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and their online presence on Health Unlocked https://healthunlocked.com/cllsupport . The association is supported and generously funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from various pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the	**Leukaemia Care** Janssen - £20,270 (£20,000 core funding and £270 honorarium) AbbVie - £11,040 (£10,000 core funding and £1,040 honorarium)

comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	AstraZeneca UK - £650 honorarium Gilead Sciences - £10,000 emergency funding Pfizer - £10,000 support services **Lymphoma Action** Janssen-Cilag - £8,000 for digital patient support, Live Your Life and publications. AbbVie - £12,000 for education programmes for people affected by lymphoma. AstraZeneca UK - £40,000 for health inequalities and digital patient support. Gilead Sciences - £10,000 for publications. Roche Products - £25,000 for digital patient services and TrialsLink. **CLL Support Association** Janssen - £7,500 Astrazeneca - £14,000 Abbvie - £12,000 Astrazeneca – £10,000 Roche – £15,000 Gilead – £15,000 Astrazeneca – £15,000 All general support
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information for this submission was gathered through a number of sources. Surveys consulted include Leukaemia Care's 2021 'Living with Leukaemia' survey alongside a new joint survey conducted for the purpose of this submission, which generated 109 responses from CLL patients. We then conducted several patient interviews with people who had experience of ibrutinib with venetoclax, which generated quotes we have used

	in the submission. Additional quotes were gathered through other one-to-one patient discussions, analysing patient stories, support groups and from patient panel meetings.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	*Patient experience* Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia. The risk of developing CLL increases with age, it is most common in older adults, with a median age at diagnosis of between 67 and 72 years. Taking into consideration the physical, emotional and financial impact on CLL patients as well as the impact on their carers, a CLL diagnosis greatly affects a patient's quality of life. Patients recently told us: *"Being told was a bad experience. As soon as I heard the word leukaemia …My grandmother had leukemia and she went into hospital and never came out again. I thought the world had stopped"* *"The prognosis was on the screen when he told me. I thought I was going to be dead and buried"* *"It was a huge shock at diagnosis! Incredibly scary. There were no support groups. I eventually learned to put it back in its box between appointments."* From diagnosis, CLL has a negative impact on an individual's mental health. The 2017 'Living with Leukaemia' Survey from Leukaemia Care reported 38% of CLL patients felt more anxious or depressed since diagnosis. Patients can sometimes feel they are a burden to carers which also has a knock-on effect for both their physical and mental health. One CLL patient commented "*After being discharged from hospital I decided not to worry my family and kept things bottled up. Looking back now that was the wrong decision."* CLL patients are especially prone to relapsing-remitting and, as CLL is incurable, patients will often be thinking about their next treatment and worrying about what challenges this might bring, including whether it will work in bringing about a response. A CLL patient we spoke to who has had multiple lines of treatment said *"To live with CLL, every day you know you cannot be cured of this cancer"*. The ongoing stress and mental health impact of CLL treatment on the patient as well as their family, friends and carers can therefore also be significant. Living with untreated CLL often also has physical side-effects for patients, such as fatigue, fever, night sweats, weight loss, weakness etc. Furthermore, CLL patients who receive active treatment, such as intensive chemotherapy, will experience a range of additional side-effects, which can negatively affect patients physically in both the short-term and the long-term.

	It is also necessary to note the financial impact living with CLL has on the patient, due to time taken off work, reducing work hours or retiring and increased costs of travel to appointments, parking costs etc. One CLL patient said *"So, for my colleagues at work, knowing the news of my chronic condition, it was business as usual after a while. I tried to make it for myself too. Of course, my body wouldn't have it and the fatigue got worse over time, so I eventually resigned".* Those with CLL have an increased risk of infections due to their immune systems being compromised. Infection risk can be worsened by treatment too *"During my treatment I suffered from many infections which results in admission to hospital. So, after my treatment I was very weak and could not walk very far and was always tired*". Infections are the second highest cause of death related to CLL after disease progression (Strati P, Parikh SA, Chaffee KG, et al., 2017). This means patients have to take extra precautions, affecting their lives, to protect themselves, which undoubtedly has a negative effect on patients who are not able to engage with society as usual and can feel isolated. *Carers' experience* One CLL patient describes the psychological impact her CLL diagnosis had on her husband, saying "*he kept things to himself, he wouldn't speak to anyone".* Other CLL patients have told us that it can sometimes be harder for the person supporting the patient than for the patient themselves, as they need support in different ways, and this is often not readily available.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Currently for people without a 17p deletion or TP53 mutation who are also fit enough to receive intensive chemotherapy, FCR remains a main comparator in this setting. The only other option these patients without mutations who are fit for FCR have is venetoclax with obinutuzumab, but this is still in the Cancer Drugs Fund in this setting and is therefore not routinely available yet. While FCR is often effective for this group and can achieve enduring remission, downsides such as its side effects are not favoured by patients. Intensive chemoimmunotherapy, like FCR, also comes with a risk of significant long-term side effects, such as continued cytopenias, MDS or secondary cancer development. These undoubtedly have an extremely negative impact on patients who are currently taking FCR and are worried about the future or who are in fact experiencing these long-term side effects. One patient described their experience with FCR below: *"When my CLL needed 1st treatment, being a younger fit CLL patient, all that was available to me at that time was FCR. Before I started treatment I was very worried about potential long term issues…this caused me some considerable anxiety before treatment. Unfortunately this fear was justified by my experience of FCR treatment itself. FCR treatment made me feel very unwell…I became pancytopenic and was transfusion dependent after two treatment cycles. Unfortunately the treatment had to be stopped because of this, leaving me without a durable remission and with what have proved to be long term immunity issues that cause me problems today and require regular immunoglobulin infusions to help manage this, which I understand is for life. The resulting short and long term impact of FCR treatment on me can still make me very anxious."* For CLL patients with a 17p deletion or TP53 mutation the options are more limited to idelalisib with rituximab, acalabrutinib, venetoclax with obinutuzumab or ibrutinib monotherapy for patients who are unsuitable for chemotherapy. However, 3 out of 4 of these treatments are continuous therapies, and our survey revealed that the majority of respondents (59.6%) would prefer a fixed duration treatment and only 4.6% would prefer continuous therapy. Furthermore, monoclonal antibodies (e.g., obinutuzumab or rituximab used in combination with venetoclax) can also have quite severe side effects and are therefore not always suitable for more frail patients. Additionally, co-morbidities are a consideration, as drugs like acalabrutinib can result in serious heart complications for patients who have any existing or unknown heart conditions. Many of the existing treatment administration methods for both those patients with and without deletions/mutations are not considered convenient. For example, venetoclax obinutuzumab involves intravenous administration, which is invasive and requires patients to travel to hospital more frequently. Having a convenient method of treatment delivery (e.g., oral tablets), was ranked by 53 (48.6%) of CLL patients in their top 3 most

	important features of a treatment, out of a total of 8 features. It was tied with CLL no longer being detectable in your blood.

8. Is there an unmet need for patients with this condition?	In our most recent survey for the purpose of this submission when asked if they think existing CLL treatments are sufficient, 78.7% of CLL patients responded either no or not sure. There are unmet patient needs across all potential subgroups and all deserve ibrutinib with venetoclax to be an option for them. Despite there being a number of existing options for treatment in the untreated CLL setting, it was clear from the survey we conducted for the purpose of this submission that CLL patients would like more options and greater choice. When asked where the unmet need lies, CLL patients commented *"the UK seems to be behind with treatments on offer in other countries", "researching and bringing out new drugs and new drug combinations is important"* and that there needs to be *"further research into new treatments"*. As CLL is incurable, patients are aware that they might have to try many if not all of the treatments on offer over time, as current treatments stop becoming effective or are no longer tolerable. Our survey revealed many patients thought the absence of a cure was an unmet need. One CLL patient from a previous survey claimed *"my view is a cure is a non-specific term, 'cause all it says is that you are kept alive long enough until you die of something else."* To them a cure does not mean you are disease free, but rather that there are enough treatment options to keep you alive until you die from something not related to CLL. Therefore, for as long as we are not able to provide a cure for patients we at least need to make as many treatment options available as possible, including in the first line setting. Furthermore, patients would like access to more effective and combined treatments in the first line. Patients told us "*the access to combination treatments would help instead of having to fail each treatment before getting the next", and w*hen asked what they feel is not being addressed by current treatment options, one patient said *"more choices of types of treatment and possibly the option of mixing more medications (currently just O+V, it might be great to have options like I+V or O+V+I)"* (nb. O refers to obinutuzumab, V to venetoclax and I to ibrutinib). There are fewer existing treatments for those patients with a 17p deletion or TP53 mutation than there are for those without these abnormalities and it's possible that none of the treatments currently on offer work for all of these patients. One patient highlighted that *"there also needs to be more therapies for the high risk CLL patients".*

	As mentioned above, many of the treatments on offer (including 3 out of 4 of the treatments for genetically high-risk patients) are continuous therapies, which creates an unmet need for more treatments which are fixed duration. This is also important as a large proportion of patients are unable to continue taking continuous therapies by the 5-year mark. 50% of patients may have to discontinue a continuous therapy due to long term side effects, long term toxicity or because they have become refractory to the treatment. Lastly, as mentioned above, many of the treatments on offer including comparator venetoclax with obinutuzumab involve intravenous administration. This creates the need for greater options of treatments which have convenient administration methods, which cause less disruption to patient's daily lives.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Ibrutinib with venetoclax provides an all-important additional option for patients and clinicians alike. Clinicians prefer to have greater options when it comes to the treatment of CLL, especially as these patients are prone to relapse/remitting and this allows doctors to create more personalised and tailored treatment plans. Not only is ibrutinib with venetoclax another option in a setting where having as many options as possible is particularly valued, but it has many preferable treatment characteristics which improve patients' experience of treatment and care, and which many of the existing treatments do not have. With regards to side effects, ibrutinib with venetoclax is not as intensive as other treatments, such as FCR, and patients are less likely to suffer from long-term side effects. We surveyed and spoke to a number of people who had tried ibrutinib with venetoclax and while some patients did report expected and likely short-term side effects, one patient commented they had *"no noticeable side effects yet so I am currently tolerating the treatment well. I am able to work… I have heaps more energy and am basically able to function normally".* Clinical trials have revealed that ibrutinib with venetoclax is effective at achieving MRD negativity (more so than comparator chlorambucil with obinutuzumab). When we asked a CLL patient in a focus group how they would define a cure in CLL they responded, *"Oh gosh, MRD negative for a very long… you just never come out of MRD negative I suppose"*. Another patient told us "MRD is a goal and I'm sad not to have reached it after 2 and a half years", which reinforces the need for more effective treatments in the first line. All untreated CLL patients deserve the chance to achieve MRD negativity. We surveyed and spoke to a number of people who had tried ibrutinib with venetoclax and their personal experiences of treatment are overwhelmingly positive in that many have achieved MRD negativity: *"The results were extremely good fairly quickly, lymph node swelling reduced and wbc reduced dramatically within months. I'm still on this treatment and have reached UMRD within 3 years".* *"Very quickly effective, then reached Urmd within a year"* *"The advantages of taking Ibrutinib were, oral dosing and taken at home, also rendered me MRDu in peripheral bloods quite quickly."* The CAPTIVATE clinical trial also showed that when treated with ibrutinib with venetoclax at 24 months, progression-free survival was 95% and overall survival (OS) was 98%. The duration of time that the disease is stable and does not progress was the number 1 ranked important feature of a treatment by patients in our survey.

	Ibrutinib with venetoclax is also advantageous because it is oral (tablets) with 65% of CLL patients in our 'Living with Leukaemia survey 2021' saying it is their preferred treatment method (followed by 28% oral (dissolvable tablet). The patients we spoke to who had direct experience of ibrutinib with venetoclax told us about the impact convenient oral treatments have had on their lives: *"Advantages include taking tablets at home with relatively few side effects. Life for me has continued pretty much as normal."* *"No chemo and able to take at home so fitted into my daily routine"* *"Apart from the ramp up of the Venetoclax this treatment does not require frequent hospital visits. This means less stress on nursing resources too".* *"My choice was FCR or take my chances with FlAIR. The pro was that I did not take time of work for treatment with FCR."* Additionally oral tablets are less invasive for patients comparatively to intravenous alternatives, for example. As one patient described *"It (Ibrutinib and venetoclax) felt less invasive, less...It felt like the better option. I think it was the best option of the Flair trial".* Ibrutinib with venetoclax is a fixed duration treatment, which is preferred by the majority of patients we surveyed, as outlined in previous sections. Currently there are more limited treatments available to untreated CLL patients which are fixed duration, so ibrutinib with venetoclax fills this gap.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	While a couple of patients reported they had no side-effects from ibrutinib with venetoclax, some patients in our survey commented that they did experience side effects including, “slight side effect (mild headaches)”, “severe facial red spots, sore throat, mouth ulcers, sickness and STVs”, "ongoing gastric issues and recurrent urine infections” etc. Two patients experienced more severe side effects, with one patient having to stop taking ibrutinib due to side effects after 12 months. However, both these patients did in fact achieve MRDu. In our ‘Living with Leukaemia’ 2021 survey, the majority of CLL patients said they would be willing to experience additional side effects for a more effective treatment. When asked for their thoughts on combination treatments in the survey, some patients told us that while they imagine it to be more effective, they would be concerned about increased side effects with two drugs: *“A combination may be more effective than a single treatment, but it is twice as much medicine to take and possibly two lots of side-effects to deal with”.* However, ibrutinib with venetoclax is not as intensive as some chemotherapy options in this setting and the CAPTIVATE study determined the safety profile of the combination of ibrutinib with venetoclax as being generally consistent with known adverse events for each agent separately and that no new safety issues were identified. While the majority of patients we spoke to did achieve MRD negativity with ibrutinib with venetoclax, one patient did not: “*MRD is a goal and I’m sad not to have reached it after 2 and a half years”.* Unfortunately, not every treatment will work for everyone, but this further emphasises the importance of increased options for CLL patients across the board. It could, however, be worrying for patients who might not achieve MRD negativity from ibrutinib with venetoclax and who will be wondering whether this limits their future treatment options, i.e., retreatment with either of the agents in the future. 76.9% of patients surveyed said that at the time of their first treatment, they would consider the impact of their initial treatment on their future treatment options. *“My concern is what happens if you relapse after being treated by FCR, a BTK Inhibitor and venetoclax. What is next?”* However, it has not yet been clinically determined whether retreatment with ibrutinib and/or venetoclax is an option, and with a good overall response from the treatment in the first line, not that many patients will relapse. Furthermore, there are other options in future treatment lines, such as BTKIs.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All CLL patients would benefit from having ibrutinib with venetoclax as an option in the first-line setting and all patients deserve to have this treatment available to them. Some (e.g. those without mutations) due to the fact it provides a less intensive alternative without common long-term side effects, and others (e.g. those with mutations), because it is a fixed duration treatment, unlike many of the alternatives for this group. Further detail of the various reasons why each group would benefit can be found earlier in this submission.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/a

Other issues

13. Are there any other issues that you would like the committee to consider?	N/a

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A CLL diagnosis has a significant impact on patients' quality of life • There is an unmet need in all CLL patients, as other treatment options in the setting can be either unsuitable, ineffective or intolerable, and can have long-term side effects. • More options are needed up front for all patients, with improved treatment characteristics. • Ibrutinib with venetoclax is both an oral (tablet) treatment and fixed duration, both of which are valued highly by patients. There is also less chance of long–term side effects. • Ibrutinib with venetoclax is effective at achieving MRD negativity, which CLL patients liken to a "cure".

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Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK CLL Forum and British Society of Haematology
3. Job title or position	Consultant Haematologist [redacted] and member of British Society of Haematology
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKCLL Forum was established by late Prof. Terry Hamblin in 2000 as an charitable organisation for CLL in the UK. Its aims remain, to bring together everyone with an interest in CLL and in particular to bridge the gap between the clinical and scientific aspects of the disease. In doing so, the Forum provides an ideal framework within which the entire UK CLL community can input into issues such as guidelines, clinical trials and translational science. The British Society for Haematology (BSH) has been bringing haematology professionals together since 1960 to transform the care our members provide to patients. With over 2500 members worldwide, we are the largest UK haematology organisation and the only society to cover all aspects of the specialty. BSH is an independent organisation that is funded primarily by the membership fees of its members and charitable money. Listening: Members work together to share ideas and knowledge, and to champion and strengthen haematology practice Learning: Help shape the future of haematology by providing access to resources, events and education that support your professional development Leading: Bridge the gap between research and practice, our guidelines raise the standards of clinical and patient care

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	UK CLL Forum receives educational grants from some of the relevant manufacturers aimed at organisation of independent scientific meetings. Amounts received in the last 2 years are outlined below: **14/04/2021** Direct credit Roche 2500.00 **26/05/2021** Direct credit Astra Zeneca 10000.00 **17/06/2021** Direct credit AbbVie 5000.00 **21/06/2021** Direct credit Incyte 500.00 **23/09/2021** Direct credit Roche 3500.00 **28/10/2021** Direct credit Incyte 500.00 **11/11/2021** Direct credit AbbVie 5000.00 **23/11/2021** Direct credit Janssen 3500.00 **17/12/2021** Direct credit Eli Lilly 500.00 **24/02/2022** Direct credit AbbVie 5000.00
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	CLL is a cancer characterised by uncontrolled proliferation of lymphocytes within the bone marrow and/or lymph nodes. This leads to progressive bone marrow failure and/or worsening lymphadenopathy. The aim of treatment is to induce remission by clearing disease within the bone marrow and nodes and improve both progression free and overall survival. There is no cure currently for CLL and treatments have limited efficacy and associated toxicities, hence improvement of quality of life, minimisation of effects of disease (e.g. reduce incidence of infections, response to vaccinations) are also relevant treatment goals. This can be achieved with continuous therapy that leads to sustained disease control or with time-limited therapy that achieves deep responses. Survival has improved over the latest decade, making the impact of therapies on longer term effects such as secondary cancer, cardiovascular health and Richter's transformation increasingly important.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Response in CLL is measured by the internationally standardised IWCLL criteria (International Workshop on Chronic Lymphocytic Leukaemia). It is generally accepted that partial or complete responses are acceptable (i.e. resolution of lymphadenopathy and bone marrow function), provided they are accompanied with resolution of CLL-related symptoms. Minimal residual disease (MRD) is a concept that refers to very deep CLL remissions in the blood and bone marrow, demonstrated using multi-colour flow cytometry or next generation sequencing, these are not yet established treatment goals but will likely be introduced in the coming years. The most recent randomised trials that have evaluated this technology use MRD as an efficacy endpoint. It has been demonstrated that MRD negativity correlates with improved PFS and OS and we also know that the presently appraised technology is capable of inducing such deep remission in a considerable proportion of patients.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The treatment of CLL patients who fail all existing and available drug-classes remains the biggest unmet need. Despite the recent approval of novel agents for treatment of CLL, which are now readily available in the treatment pathway, there is still a significant subgroup of patients for whom treatment options are exhausted and who die of progressive CLL, this is particularly important in patient with poor-risk disease at diagnosis (ie TP53 aberrations). The main aspect that the present technology aims to address is whether the combination of two of the novel targeted agents for CLL, used in combination, will improve patient outcomes. This is opposed to the use of each of the agents individually in sequence. The unmet need in this circumstance is the lack of evidence regarding the best sequencing strategy of patients with CLL. There are other relevant unmet needs pertaining standard disease characterisation at baseline and post treatment assessment, namely, the need for standardised and accessible IGHV analysis ahead of first line therapy and the incorporation of minimal residual disease (MRD) evaluation into routine practice. It has been now widely demonstrated in large randomised Phase 3 trials that MRD negativity predicts for longer PFS *(Kater et al, J Clin Oncol, 2020, 38(34):4042-4054, Wierda et al, J Clin Oncol, 2020, 39(34): 3853-3865, Shananfelt et al, N Engl J Med 2019; 381:432-443).* MRD can be used as a therapeutic goal, as a tool for tailored therapy and as a tool for disease monitoring/early diagnosis of relapses.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In general terms, CLL front-line treatment can be offered to patients with either combination of AntiCD20 antibody and the BCL2 inhibitor Venetoclax, or BTKi inhibitors such as Ibrutinib or Acalabrutinib, depending on the age/suitability for chemoimmunotherapy and TP53 disruption (Deletion 17p and/or TP53 mutation). Chemoimmunotherapy remains an alternative for CLL patients who are fit and are *IGHV*- mutated.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The British Society of Haematology (BSH) for the treatment of CLL. The UK CLL forum has taken a central role in the development of the updated guidelines, which incorporate acalabrutinib and venetoclax-based regimens, recently appraised by NICE and commissioned by NHSE (Walewska et at, BJH, 2022). Internationally, European Society of Medical Oncology (ESMO) guidelines (Eichhorst B, et al. Ann Oncol 2020; 32 (1):23-33) are the most frequently referred to.

	Additionally, the iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL are also relevant.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined and follows, in England, the algorithms published in the CLL guidelines. There are differences in commissioning in N. Ireland, Wales and Scotland that may result in variations of this treatment pathway. CLL is treated with B cell receptor pathway inhibitors (principally BTKi such as ibrutinib and acalabrutinib) and venetoclax (in combination with anti-CD20 monoclonal antibodies or as monotherapy) in sequence. Chemo-immunotherapy is now rarely used following studies showing major superiority of non-chemotherapy regimens over these newer treatments, which have been assessed in a number of previous technology appraisals (TA359, TA429, TA487, TA561, TA663, TA 689). Venetoclax single-agent therapy has been also recently re-appraised by NICE [TA796] and remains an option for patients with TP53 disruption on whom B-cell receptor pathway inhibitor is unsuitable, or those whose disease has progressed after both chemo-immunotherapy and/or a B-cell receptor pathway inhibitor irrespective of TP53 status. The current proposed BCSH first line rRecommendations are: (NICE approved) Venetoclax-obinutuzumab (VenO) or acalabrutinib are recommended and NICE-approved options as initial therapy in patients unsuitable for CIT irrespective of TP53 status. Bendamustine or chlorambucil-based CIT are no longer recommended. NICE-approved treatment options for fit patients with TP53 disruption include acalabrutinib, ibrutinib or venetoclax monotherapy for those with a contra-indication to B-cell receptor inhibitor. Acalabrutinib is recommend for patients who have intact TP53 and for whom FCR or BR are considered unsuitable. For fit patients with intact TP53, VenO may be obtained via CDF. For fit patients with intact TP53 and with mutated IGHV, chemo-immunotherapy with FCR remains an acceptable initial therapy
9c. What impact would the technology have on the current pathway of care?	The technology will offer a fixed-duration treatment regimen than combines the two most active therapeutic alternatives for CLL at present, whilst excluding the AntiCD20 antibodies from the front-line setting. The responses and depth of remission achieved by the combination of drugs in the appraisal are encouraging, particularly in the TP53 disrupted and the IHGV unmutated subgroups in which deep responses have been

	observed; the follow-up is still short to determine whether or not the combination of these agents as opposed to the sequential use of them as it is currently done will derive in an overall survival benefit. The GLOW study (Kater et al, NEJM, 2022) evaluated I+V vs Rituximab-Chlorambucil in elderly CLL population in a randomised phase 3 design. Results are encouraging, showing 24-month PFS of 84% for I+V combination, with 54% of undetectable MRD at 3 months post-treatment and 49% as 12 months post-treatment. Similarly for younger patient I+V has been evaluated in comparison to Ibrutinib monotherapy in a randomised phase 3 study (FLAIR, EHA2022 abstract S145), showing preliminary efficacy based on MRD determination. 71% of patients achieved MRD negativity at 2 years. Overall response and complete response rates were 88% and 59% respectively at 9 months post randomisation. FLAIR trial featured specific stopping rules for venetoclax therapy based on MRD determinations, with a minimum of 2-years of treatment. Both FLAIR and GLOW studies have excluded TP53 disrupted patients. Data for efficacy of I+V on TP53 disrupted patients is available form CAPTIVATE study (Tam et al, Blood, 2022). This is a randomised phase 2 study evaluating a fixed-duration I+V regimen in comparison to a MRD-driven duration of therapy. In the fixed duration arm of the study, 27 patients with TP53 disruption were included, CR rate was 56%, MRD was achieved in 81% in peripheral blood and 24-mnth PFS was 84%. Despite low number of patients the measurable outcomes seem numerically very similar to those achieved in the non-TP53 aberrant patients. The potential benefit of I+V combination should be evaluated in each of the below circumstances individually: -Patients fit for chemoimmunotherapy (FCR or BR) and mutated *IGHV*: These patients could be still offered chemoimmunotherapy given excellent results demonstrated for FCR in E1912 study (Shanafelt, NEJM, 2019) amongst others. With this premise, FCR comparator as will be seen in the FLAIR study remains theoretically valid. However, in practice, these patients can be offered Venetoclax/Obinutuzumab as per most recent NICE guidance [TA663]. -Patients fit for chemoimmunotheray and *IGHV* unmutated: For these patients, current practice is to offer Venetoclax/Obinutuzumab fixed duration regimen [TA663], hence, FCR comparator of the FLAIR trial will be inappropriate to evaluate the impact of this technology in the current pathway of care.

	-Patients unfit for chemoimmunotherapy irrespective of *IGHV* mutational status: These patents are currently offered either acalabrutinib [TA689] or Venetoclax/Obinutzumab [TA663]. Similarly, the comparator arm of the GLOW study, whose baseline characteristics match this subgroup of patients, is inappropriate to evaluate the impact of the technology on the pathway of care -Patients with *TP53* aberration: For these patients the current treatment would be BTKi monotherapy or Venetoclax/Obinutuzumab, the former favoured. The results of the CAPTIVATE study will inform this evaluation, however, numbers are small and the study has no direct comparison to BTKi, hence conclusion about efficacy of I+V in this patient population cannot be drawn from the existing data for I+V therapy. Hence, evaluation of the impact of this technology in the 4 scenarios described above will require NMA and/or adjusted indirect comparisons incorporating the suitable comparators. Information on the efficacy of sequencing of treatment remains insufficient to establish efficacy of re-exposure to these drug classes at relapse after a theoretical use of fixed-duration I+V in the first line setting. Preliminary evidence suggest efficacy is retained for Venetoclax after fixed-duration regimens (Thompson et al, Blood Avd, 2022) and it is likely that BTKi also retain efficacy following the same principle, hence, we believe the use of BTKi and Venetoclax based therapies should remain an alternative for subsequent lines of therapy if I+V was favourably recommended.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The delivery of the treatment will be done within routine NHS clinical practice, both compounds have been used extensively by CLL clinicians around the country. There are no particularities of the combination in terms of treatment delivery. It remains to be clarified if the technology will apply a blanket fixed treatment duration. Some of the clinical studies that have investigated the combination, have been designed with clear rules for stopping therapy, in the majority of them, guided by MRD assessments. In order to guarantee the outcomes of the trials to the potential patients treated with this combination, a design that utilises similar MRD-driven criteria will be critical.
10a. How does healthcare resource use differ between the technology and current care?	There is a minor increase in adverse events with the combination, particularly in the elderly (>75 years) population which will also be a consideration. Most frequent adverse events of the combination are infections, diarrhoea and decreased of neutrophil counts which adds to the already widely known side effect profile of BTKi, of which the bleeding, atrial fibrillation and other cardiovascular complications are most relevant.

	The I+V combination will obviate the need for intravenous administration of Anti-CD20 antibodies which will also likely diminish health resource use as compared to fixed-duration Venetoclax/Obinutuzumab. Finally, the incorporation of MRD determination into the evaluation of response to this technology would impact the health resource use, as this is a technique that is not readily available in most centres.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Ibrutinib and Venetoclax should be available treatments for CLL in both the untreated and relapsed setting. In accordance to its current use, the present technology should be restricted to use under specialised care of a qualified and registered Haematologist or Oncologist.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There is no anticipated investment needed for the introduction of the new technology, unless the MRD determination becomes a criterion for treatment interruption, following the clinical study design. As mentioned, many centres do not have MRD availability. Nonetheless the implementation and standardisation of MRD determination will be relatively straight-forward in centres who have flow-cytometry capability for diagnostic histopathology. There are clear guidelines for MRD testing using flow cytometry available (Rawstron, Leukemia, 2016).
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This is a question that is impossible to fully answer at present, in view of the short follow-up time of the trials that have used the combination in the frontline setting, however this combination offers potentially deeper responses for patient with genetically poor risk disease, who would otherwise experience a shorted PFS to currently available therapies. The combination of I+V has yielded preliminary higher rates of complete remission and undetectable MRD in younger patents fit for CIT, when compared to BTKi or Venetoclax/Obinutuzumab regimen (Al-Sawaf et al, Lancet, 2020), hence it is likely to result in an extension of progression free survival in this subgroup. In the GLOW study, on the contrary, the rates of complete remission and undetectable MRD were lower than those reported in the CLL14 study (Venetoclax/Obinutuzumab), which could be explained by a high rate of discontinuation (25%) on the I+V arm. It remains to be seen if the long-term PFS of I+V in GLOW will be comparable to that obtained with Venetoclax/Obinutuzumab, despite the discontinuation rate.
11a. Do you expect the technology to increase length of life more than current care?	In CLL overall survival is largely affected by the subsequent lines of therapy received, which in general terms are very effective and provide long term remission. Since introducing targeted therapies we have seen improved life expectancy comparable to that of normal population https://hmrn.org/factsheets#chronic_lymphocytic_leukaemia

11b. Do you expect the technology to increase health-related quality of life more than current care?	The current appraisal, as a combination treatment, carries a higher risk of drug-related adverse events for the treatment duration, hence having a negative impact on life quality. This impact we believe is then balanced by treatment discontinuation, which effectively spares patients of the long-term risk of adverse events that continuous BTKi therapy carries, which unfortunately include cardiac sudden death in 0.5% of patients (FLAIR trial, ASH 2021 meeting, abstract 2636)
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Theoretically two subgroups of patients could have a differential effect with I+V. These are the TP53 aberrant patients and elderly patients unfit for chemoimmunotherapy, For TP53 aberrant, despite excellent outcomes of BTKi therapy, the duration of response has been demonstrated to be lower than the TP53 intact counterpart, hence it is possible that the addition of venetoclax increases efficacy of BTKi alone, the preliminary results of CAPTIVATE study suggests this might be the case. For the elderly, as mentioned before, the apparent lower efficacy of I+V in terms of CR rate and undetectable MRD rates is influenced by the discontinuation risk of the study. If these observations were replicated by other studies, there will be a theoretical reduction in the CR and MRD negative rates. Despite this, PFS could remain comparable, longer follow-up of the GLOW study will shed light into this mater. I+V regimen, provided early results are confirmed with longer follow-up, will help to fill an unmet need for the poor risk disease group (TP53 aberrant and IGHV unmutated).

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Single elements of the technology are already in use. Initial dose escalation requires multiple hospital visits over a 5-week period. There are no standard blood tests required for the administration of I+V. The management of side effects derived from therapy is likely to be similar to that of the individual components of the regimen. These are well known from an already broad experience with BTKi and BCL2i in the CLL community.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The studies of the combination of drugs that is being appraised, have used MRD as a primary endpoint and a decision-making tool to tailor treatment according to MRD status. It will remain a matter of debate during the appraisal if mandate/commissioning of MRD is likely to be possible and hence, stopping rules for I+V can be considered as part of the recommendations.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There are two potential health-related benefits that might not be included in QALY assessments. In the first instance, the psychological benefit of a fixed-duration therapy that will allow patients to return to a more normal lifestyle after treatment. This will only apply to patients who would opt for a BTKi as first line alternative. Secondly, in this same group of patients in whom a BTKi would be the alternative therapy, fixed duration therapy will reduce the pharmacological pressure exerted to the CLL clones with continuous therapy, resulting in a theoretical reduction on the emergence of resistant clones during therapy. Additionally, younger patients within the poor risk category pose a significant economic burden to the health system, evolving to exhaust lines of treatment and ultimately necessitating an allogeneic stem cell transplantation. A demonstrated PFS benefit on the poor-risk CLL with I+V combination, effectively delaying the exhaustion of lines of therapy (and with it the need for stem cell transplantation), will derive in a substantial health-related benefit for this patient.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Combination therapy is the natural evolution of the treatment alternatives for CLL. Given that two highly effective drug classes are available, the idea of combination and with it, synergistic activity against CLL clones, has a strong rationale. The available results of several studies using I+V combination as well as other BTKi and BCL2i combinations are a reflection of this rationale.
16a. Is the technology a 'step-change' in the management of the condition?	Combination therapy is the natural evolution of the treatment alternatives for CLL. Given that two highly effective drug classes are available, the idea of combination and with it, synergistic activity against CLL clones, has a strong rationale. The available results of several studies using I+V combination as well as other BTKi and BCL2i combinations are a reflection of this rationale.
16b. Does the use of the technology address any particular unmet need of the patient population?	No other particular unmet need apart from what has been mentioned so far.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	An increase in adverse events, as discussed above, is likely to increase healthcare resource usage during the time of treatment (i.e. informal clinical reviews and outpatient appointments), as compared to each of the drugs individually. This is likely also like to negatively impact life quality. However, health-care utilisation for BTKi has been evaluated in the past as continuous therapy, with the present technology, the use of resources in the context of 1-year fixed duration therapy will be considerably less. The rate of discontinuation (overall and due to AE) of the GLOW study will have to be carefully evaluated to model the patient quality of life implications of I+V.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The design of the clinical trials predate the recent approval of Venetoclax/Obinutuzumab and acalabrutinib regimens, which have displaced chemoimmunotherapy as preferred first line therapy, rendering the comparator arm of the trials non-relevant for current UK practice
18a. If not, how could the results be extrapolated to the UK setting?	The evaluation of I+V will have to rely on indirect comparisons based on the results of the active arm of the CLL14 trial (Venetoclax/Obinutuzumab) and ELEVATE-TN (acalabrutinib).
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Currently both the progression free survival and the rate of MRD negativity are clinically meaningful outcomes that have been consistently included in all trials evaluating I+V.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Follow-up of the I+V clinical trials remains short, however, no new adverse events/safety signals have been observed so far with the combination.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The evidence presented or the UK NCRI's FLAIR trial, has not yet been published and has come for meeting abstracts and presentations.

20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA174, TA216, TA343, TA359, TA429, TA663, TA689?	TA216: Eichhorst B, Fink AM, Bahlo J, et al.; International Group of Investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17(7):928-942. TA343: Al-Sawaf O, Zhang C, Tandon M, Sinha A, Fink AM, Robrecht S, Samoylova O, Liberati AM, Pinilla-Ibarz J, Opat S, Sivcheva L, Le Dû K, Fogliatto LM, Niemann CU, Weinkove R, Robinson S, Kipps TJ, Tausch E, Schary W, Ritgen M, Wendtner CM, Kreuzer KA, Eichhorst B, Stilgenbauer S, Hallek M, Fischer K. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020 Sep;21(9):1188-1200. TA689: Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, Kamdar M, Munir T, Walewska R, Corbett G, Fogliatto LM, Herishanu Y, Banerji V, Coutre S, Follows G, Walker P, Karlsson K, Ghia P, Janssens A, Cymbalista F, Woyach JA, Ferrant E, Wierda WG, Munugalavadla V, Yu T, Wang MH, Byrd JC. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia. 2022 Apr;36(4):1171-1175.
21. How do data on real-world experience	No real-world data available for I+V to comment on.

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	We foresee no equality issues with this appraisal.
22b. Consider whether these issues are different from issues with current care and why.	We foresee no equality issues with this appraisal.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Combination therapy is the natural evolution of treatment options for CLL. Given that two highly effective drug classes are available, the idea of combination and with it, synergistic activity against CLL clones, has a strong rationale. • The technology will offer a fixed-duration treatment regimen than combines the two most active therapeutic options for CLL at present, while excluding the AntiCD20 antibodies from the front-line setting. The responses and depth of remission achieved by I+V combination are encouraging, in particular for the poor risk CLL (TP53 disrupted and IGHV unmuted). However the follow-up is still short to determine whether or not the combination of these agents (as opposed to the sequential use of them as is current routine practice) will derive in an overall survival benefit. • The technology is set to be evaluated in 4 scenarios as described in question 9c. The control arms of the studies investigating I+V are irrelevant for current UK practice as these are based on chemoimmunotherapy. Hence, evaluation of the impact of the technology will require NMA and MAIC using the active arms of treatments currently approved for first line therapy in each of these circumstances. • The studies of the I+V combination have used MRD as a primary endpoint and a decision-making tool to tailor treatment according to MRD status. It will remain a matter of debate during the appraisal if mandating/commissioning of MRD is likely to be possible, and hence stopping rules/treatment extension for I+V can be considered as part of the recommendations. • The delivery of the treatment will be done within routine NHS clinical practice; both compounds have been used extensively by CLL clinicians around the country. There are no particularities of the combination in terms of treatment delivery.

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Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma [ID3860]

Produced by Aberdeen HTA Group

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Rider on responsibility for report

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Contribution of authors

Moira Cruickshank and Mari Imamura summarised and critiqued the clinical effectiveness evidence presented in the company's submission; Dolapo Ayansina and Sachin Kumar checked and critiqued the statistical analyses; Graham Scotland reviewed and critiqued the cost-effectiveness evidence with assistance from Corinne Booth; Paul Manson checked and critiqued the company's search strategies; Gavin Preston provided clinical guidance; Miriam Brazzelli contributed to the critique of the clinical effectiveness evidence, coordinated all aspects of this appraisal, and is the guarantor of this report. All authors contributed to the writing of this report and approved its final version.

Table of contents

List of tables

List of figures

List of abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AFT	Accelerated failure time
AIC	Akaike information criteria
ALC	Absolute lymphocyte count
AMR	Annual mortality rate
ANC	Absolute neutrophil count
ATC	Average treatment effect in the control population
ATO	Average treatment effect in the combined/overall population
ATT	Average treatment effect in the treated population
BCL-2	B-cell lymphoma-2
BCR	B-cell receptor
BIC	Bayesian information criteria
BM	Bone marrow
BNF	British National Formulary
BR	Bendamustine + rituximab
BSA	Body surface area
BSC	Best supportive care
BSH	British Society of Haematology
BTK	Bruton's tyrosine kinase
CD20	Cluster of differentiation 20
CDF	Cancer Drugs Fund
CI	Confidence interval
CIRS	Cumulative Illness Rating Scale
CIT	Chemo-immunotherapy
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine clearance

CRi	Complete response with incomplete bone marrow recovery
CSR	Clinical study report
CT	Computerised tomography
CYP3A	Cytochrome P450, family 3, subfamily A
del11q	11q deletion
del17p	17p deletion
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	European Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-3L	EuroQoL-5 Dimension-3 Levels
EQ-5D-5L	EuroQoL-5 Dimension-5 Levels
ESMO	European Society for Medical Oncology
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FC	Fludarabine + cyclophosphamide
FCR	Fludarabine + cyclophosphamide + rituximab
FD	Fixed duration
FISH	Fluorescent in situ hybridisation
FR	Fludarabine + rituximab
G-CSF	Granulocyte colony-stimulating factor
GPM	General population mortality
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSE	Health Survey for England
HTA	Health Technology Assessment
I+R	Ibrutinib + rituximab

I+V	Ibrutinib + venetoclax
ICER	Incremental cost-effectiveness ratio
IGHV	Immunoglobulin heavy chain variable region
INMB	Incremental net monetary benefit
INV	Investigator
IPD	Individual patient data
IPTW	Inverse probability for treatment weighting
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
iwCLL	International workshop on chronic lymphocytic leukaemia
KM	Kaplan-Meier
LDH	Lactic acid dehydrogenase
LDi	Largest diameter
LY	Life year
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRD	Minimal residual disease
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
Nodular PR	Nodular partial response
O-Clb	Obinutuzumab + chlorambucil
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival

PAS	Patient access scheme
PB	Peripheral blood
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Progress after next line (second line) of treatment
PH	Proportional hazards
PICOS	Population, Intervention, Comparison, Outcome, Study design
PLD	Patient-level data
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
R/R	Relapsed/refractory
RCT	Randomised controlled trial
RMME	Repeated-measures linear mixed-effects
SD	Standard deviation
SE	Standard error
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TEM	Treatment-effect modifiers
TFI	Treatment-free interval
TLS	Tumour lysis syndrome

TP53	Tumour protein 53
TSD	Technical Support Document
TTF	Time to treatment failure
TTFR	Time to first response
TTNT	Time to next treatment
UK	United Kingdom
ULN	Upper limit of normal
uMRD	Undetectable minimal residual disease
US	United States
VAS	Visual analogue scale
VBA	Visual Basic for Applications
VenO	Venetoclax + obinutuzumab
VenR	Venetoclax + rituximab
VPLD	Virtual patient-level data
WTP	Willingness to pay

1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The focus of the submission received from Janssen is ibrutinib + venetoclax (I+V) for untreated chronic lymphocytic leukaemia (CLL) in adults. CLL is the most common type of leukaemia and is often asymptomatic at first but generally uncurable.

The clinical evidence submitted by the company consists of two trials: CAPTIVATE, a phase II trial of I+V in people with no del-17p for whom fludarabine-based therapy is suitable (the FCR [fludarabine + cyclophosphamide + rituximab]-suitable population) and GLOW, a phase III randomised trial of I+V versus obinutuzumab + chlorambucil (O-Clb) in people with no del-17p for whom fludarabine-based therapy is unsuitable (the FCR-unsuitable population). At extended follow-up in CAPTIVATE (median 38.7 months), the investigator-assessed CR/CRi rate in people without del17p was 58.1% (95%CI 49.8, 66.4). Progression-free survival as assessed by the investigator in these patients at 36 months was [redacted] At extended follow-up in GLOW (median 34.1 months), independent review committee-assessed PFS at 30 months was 80.5% (95%CI [redacted] in the I+V group and 35.8% (95%CI [redacted]) in the O-Clb group (HR 0.21; 95%CI 0.13, 0.35).

The company carried out indirect treatment comparisons for the FCR suitable and unsuitable populations as there are no head-to-head data for the comparisons of I+V with FCR, VenO or acalabrutinib.

The company present a de Novo semi-Markov model to assess the cost-effectiveness of I+V in previously untreated CLL. The case focusses on three specific subpopulations defined by suitability for treatment with FCR and the presence of del17p/TP53 mutations. Comparators differ across the subpopulations. The model uses four health states: progression free in first line treatment (PF 1L), progression free in second line treatment (PF 2L), disease progression (PPS) and death. Key efficacy inputs in the model are derived from the CAPTIVATE and GLOW clinical trials and the indirect treatment comparisons. Utility and resource use inputs are derived from clinical trials, previous NICE appraisals, and other published sources.

The key issues identified by the EAG in the company's submission are summarised in Table 1.

Table 1 Overview of the EAG's keys s issues

ID3860	Summary of issue	Report sections
1.	Immaturity of OS and PFS data	3.2, 3.4, 4.2.6
2.	The approach to generating transition probabilities by extracting age/sex matched general population mortality from extrapolated PFS, leading to diminishing risks of progression in the surviving cohort (particularly in the older FCR-unsuitable cohort where background mortality is higher).	4.2.6
3.	The progression-free utility value applied in the model lacks face validity	4.2.7
4.	Applying the same utility value to the PF 2L and PPS health states may not be reflective of patients' quality of life after progressing on first-line treatment	4.2.7

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are that the EAG preferred to: 1) cap health state utility for progression free on first line treatment at general population norms; 2) apply higher utility for those progression free on second line therapy compared to those in the post-progression state; 3) apply cycle treatment costs to all those on treatment at the

beginning of each cycle (commencing in cycle zero); include costs of wastage for oral therapies.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Delaying or preventing progression of disease to more severe stages
- Reducing mortality associated with the progression of disease
- Its method of administration (oral) having a lower burden on quality of life compared to some alternative treatments requiring intravenous infusion
- Its impact on adverse events compared to other treatments

Overall, the technology is modelled to affect costs by:

- Having different acquisition and administration costs compared to alternatives
- Delaying or preventing progression to subsequent stages of disease which incur further treatment and disease management costs
- Its impact on adverse events which incur management costs

The modelling assumptions that have the greatest effect on the ICER are:

- The comparative effectiveness of the technology on progression free survival (particularly the risk of progression) compared to the alternative treatments over the model time horizon

1.3 The decision problem: summary of the EAG's key issues

In general, the company's decision problem is in line with the NICE final scope.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence presented in the company's submission and identified the following issue for consideration.

Issue 1. Immaturity of OS and PFS data

Report section	Section 3.2, 3.4
Description of issue and why the EAG has identified it as important	The data presented in the CS are immature because of the relatively short follow-up period (even with the extended follow-ups). This meant that certain assumptions (such as the proportionality of hazards long term) could not be tested even though they were used in the economic modelling.
What alternative approach has the EAG suggested?	The approach the company used for the analysis of the data is valid and appropriate, but the data limitations mean that extrapolations and subsequent comparisons are always going to be problematic and fraught with uncertainties. The collection of longer-term data could help mitigate this issue and reduce uncertainties around the effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	As there is uncertainty surrounding the effectiveness estimates provided. This in turn leads to uncertainty in the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	There is no evidence currently available that would reduce the current uncertainty resulting from the immaturity of the data. Longer-term data will be key to resolving this issue.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the cost-effectiveness effectiveness evidence presented in the company's submission and identified the following issue for consideration.

Issue 2. Generating transition probabilities for progression by extracting age/sex matched general population mortality from extrapolated PFS

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company use a Markov model. But rather than estimating transition probabilities for progression directly, they fit curves to PFS data and subtract estimates of pre-progression mortality (capped by age/sex matched general population mortality) from the extrapolated PFS curves. In the older FCR-unsuitable and high-risk populations, this leads to the estimated risk of progression diminishing to zero with more effective treatments whilst a substantial proportion of the cohort remain alive and progression free. This infers a cure for a fraction of the FCR-unsuitable and high-risk populations. The same issue does not arise in the younger FCR-suitable population where pre-progression morality is lower and, therefore, the calculated risk of progression remains above zero throughout the time horizon of the model. This seems inconsistent and is likely due to the approach to estimating the transition probabilities rather than the treatments being more effective in reducing the risk of progression (conditional on survival) in the older FCR-unsuitable and high-risk populations. There is potential for the approach to bias cost-effectiveness in favour of more effective treatments in these populations.
What alternative approach has the EAG suggested?	Given the data limitations, it may not be possible to derive reliable estimates and extrapolations of the transition probabilities of progression directly. To address this uncertainty, the EAG have explored a scenario where the transition probabilities of progression in the FCR-unsuitable and high-risk populations are not allowed to fall below the corresponding model cycle estimates for those receiving I+V in the FCR-suitable population.
What is the expected effect on the cost-effectiveness estimates?	The impact of this is that it reduces the progression free and overall survival gains of more effective versus less effective treatments in the FCR-unsuitable and high-risk populations. The cost-effectiveness findings are generally robust to this change, but there may be potential for it have greater impact if applied with other changes.
What additional evidence or analyses might help to resolve this key issue?	If more mature data become available, the company may want to explore alternative methods to estimating and extrapolating transition probabilities for progression directly from the data, rather than relying on the approach of extracting estimates of pre-progression mortality from PFS.

Issue 3. Progression-free health state utility value

Report section	Section 4.2.7
Description of issue and why the EAG has identified it as important	The progression-free utility value applied in the model lacks face validity. Although the value was derived from EQ-5D-5L data collected in the GLOW trial in a relevant patient population, the resulting PF utility value is higher than population norms and clinical expert advice to the EAG confirmed this was not realistic. This overestimates the quality of life of CLL patients who are progression-free.
What alternative approach has the EAG suggested?	The EAG's preference is to have the PF health state utility value capped at age-adjusted population norms. This is consistent with the approach taken in TA689 and TA663.
What is the expected effect on the cost-effectiveness estimates?	At clarification stage the company provided sensitivity analysis which capped the PF utility value at population norms as requested. This resulted in a PF value of 0.849 in the FCR-suitable population (age 58) and 0.798 in the FCR-unsuitable and high-risk populations (age 71). When these values were applied in the model this r3esulted in a modest increase in the ICER in the FCR-suitable population, and in the FCR-unsuitable and high-risk populations the overall direction of the results remained unchanged from the base case. There is potential for the impact to be more important if applied with other changes.
What additional evidence or analyses might help to resolve this key issue?	Additional clinical expert validation on the alternative approach would be helpful.

Issue 4. PF 2L health state utility value

Report section	Section 4.2.7
Description of issue and why the EAG has identified it as important	Applying the same utility value to the PF 2L and PPS health states may not be reflective of patients' quality of life after progressing on first-line treatment, particularly given the large difference in mortality rate between these health states. This may underestimate the utility value in the PF 2L health state where patients may experience a higher quality of life than when they progress to later lines of therapy/BSC.
What alternative approach has the EAG suggested?	An alternative approach preferred by the EAG is to use the post-progression utility value derived from the GLOW trial [redacted] for the PF 2L health state.
What is the expected effect on the cost-effectiveness estimates?	This analysis was provided by the company at clarification stage where the post-progression utility value from GLOW was applied to the PF 2L health state only. Overall, this had a small impact on the results, but may be more important when applied cumulatively with other changes.
What additional evidence or analyses might help to resolve this key issue?	Additional clinical expert validation on the alternative approach may be helpful.

1.6 Other key issues: summary of the EAG's view

The EAG considers the extrapolation of progression free survival for I+V versus its comparators to be an area of particular uncertainty due to the immaturity of the PFS data from CAPTIVATE and GLOW, and the reliance on a constant proportional hazards assumption for certain comparisons in the economic model. This is addressed through sensitivity analysis. The company present severity calculations for the condition under standard of care in all three populations covered and find that it does not meet the criteria for severity weighting in any of the populations. The EAG agrees with this finding.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the uncertainties identified and discussed in chapters 4 and 5, the EAG prefer to include the following assumptions in their based case.

1. PF 1L utility valued capped at general population norms

2. PF 2L utility value applied as a multiplicative decrement to PF 1L utility (multiplicative decrement = [redacted]))

3. First line treatment acquisition and admin costs, and treatment modality utility decrements, applied from cycle zero in the model rather than cycle one in the model.

4. Inclusion of drug wastage for oral therapies, to account for potential incomplete use of unused medicine resulting from dose intensity reductions.

Given the space requirements to show the impact of individual and combined changes on the company's ICERs for three separate populations, two with multiple treatment comparators, readers are directed to Chapter 6, section 6.2, Tables 26 to 28 to see the impact of individual changes. The cumulative impact of the combined changes is summarised in Table 2.

Table 2 Summary of the impact of the EAG preferred modelling assumptions on the ICERs

Scenario	Incremental cost	Incremental QALYs	ICER
FCR-suitable population (I+V versus FCR)			
Company base case	[redacted]	[redacted]	£8,277
EAG preferred base case combining changes 1-4 as summarised above	[redacted]	[redacted]	£11,176
FCR-suitable population: I+V versus O-Clb, VenO and acalabrutinib			
Company base case			
Vs. O-Clb	[redacted]	[redacted]	Dominant
Vs. VenO	[redacted]	[redacted]	Dominant
Vs. Acalabrutinib	[redacted]	[redacted]	less costly, less effective (£1,546,602)
EAGs preferred base case combining changes 1-4 as summarised above			
Vs. O-Clb	[redacted]	[redacted]	Dominant
Vs. VenO	[redacted]	[redacted]	Dominant
Vs. Acalabrutinib	[redacted]	[redacted]	less costly, less effective (£1,299,198)
High-risk population: I+V versus VenO and ibrutinib acalabrutinib			
Company base case			
Vs. VenO	[redacted]	[redacted]	Dominant
Vs. Ibrutinib	[redacted]	[redacted]	less costly, less effective (£675,793)
Vs. Acalabrutinib	[redacted]	[redacted]	less costly, less effective (£1,546,602)
EAGs preferred base case combining changes 1-4 as summarised above			
VenO	[redacted]	[redacted]	Dominant
Ibrutinib	[redacted]	[redacted]	less costly, less effective (£606,789)
Acalabrutinib	[redacted]	[redacted]	less costly, less effective (£1,299,198)

FCR = fludarabine + cyclophosphamide + rituximab; I+V = ibrutinib + venetoclax; O-Clb = Obinutuzumab + chlorambucil; VenO = venetoclax + Obinutuzumab

For further details of the exploratory and sensitivity analyses done by the EAG, see Chapter 6, sections 6.1 and 6.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Janssen is untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) in adults. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is ibrutinib (IMBRUVICA®).

2.2 Background

Chronic lymphocytic leukaemia is the most common type of leukaemia[1] and is characterised by clonal proliferation and accumulation of B lymphocytes in bone marrow, peripheral blood, and lymphoid tissues.[2]

Small lymphocytic lymphoma is considered a different manifestation of the same disease process as CLL and is managed in the same way as for CLL.[2, 3] SLL and CLL are considered to be a single entity in the World Health Organization (WHO) classification and will be referred to as CLL hereafter.[4, 5]

The risk of developing CLL increases with age, most commonly affecting older adults with median age for diagnosis of 72 years (IQR 64-80) in England.[6] CLL is more common in men than in women.[7]

More than 80% of patients are diagnosed as an incidental finding on a routine full blood count and remain asymptomatic at first.[3] Clinical signs and symptoms might develop as the cancer progresses and include enlarged, but painless, lymph nodes, enlarged spleen, fatigue, fever, night sweats and weight loss.[3]

In most cases, CLL remains an incurable disease and the goals of therapy are to improve quality of life and to prolong survival.[4] Patients with asymptomatic early-stage disease should be monitored without therapy, using a 'watch-and-wait' strategy.[2, 4] When treatment is

initiated, factors influencing the choice of treatment include an assessment of age, fitness to tolerate chemotherapy and/or immunotherapy and TP53 mutation status. British Society for Haematology (BSH) recommends screening for TP53 disruption (i.e. del 17p and/or TP53 mutation) prior to each line of treatment, as patients with these genetic abnormalities represent a high-risk group.[8] There are no standard criteria for determining fitness level in CLL but the CS included as the assessment of fitness factors such as age, presence and severity of comorbidities and performance status (PS) (Document B, Section B.1.1, page 10).

Chemoimmunotherapy (CIT) with fludarabine, cyclophosphamide, and rituximab (FCR) has been the standard of care for first-line treatment for fit patients with CLL and intact TP53.[8] In 2020 venetoclax in combination with obinutuzumab (VenO) became available through the Cancer Drug Fund (CDF) in the UK. Bendamustine plus rituximab (BR) has NICE approval for use in fit, younger patients without TP53 disruption but it is no longer recommended in the 2022 BSH guidelines.[8]

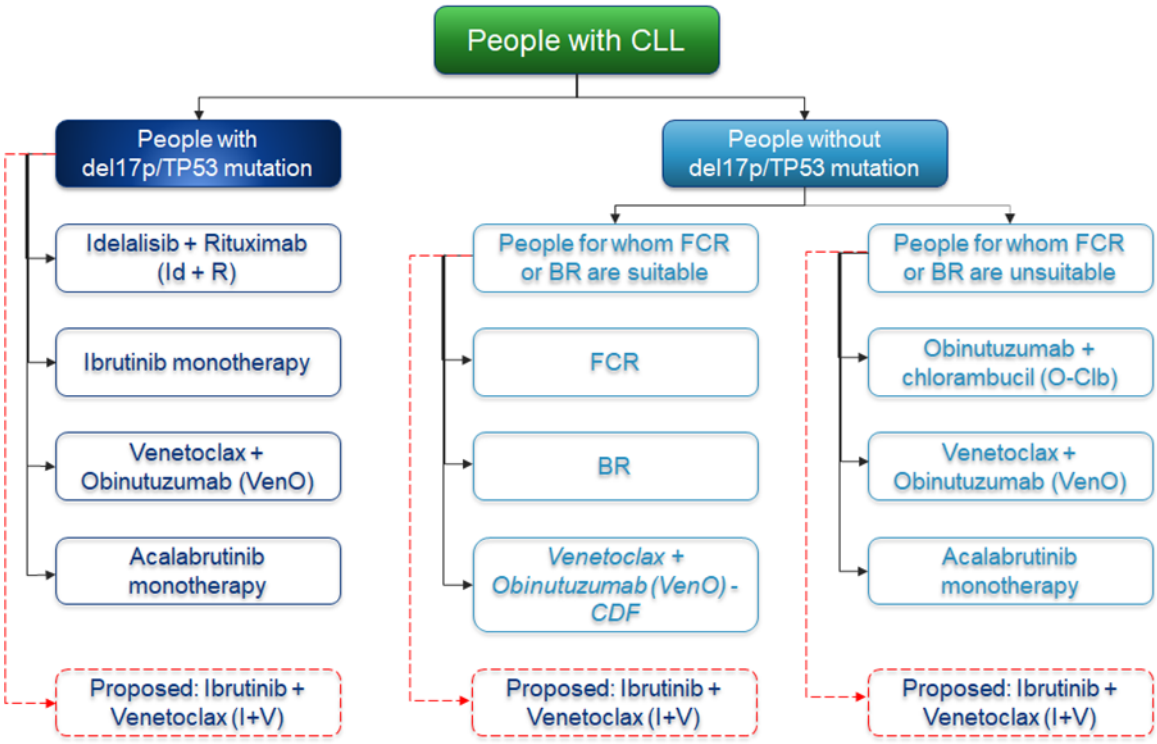
Due to the relatively higher age of CLL patients, the majority of patients are in the 'less fit' category with various comorbidities and unsuitable for FCR. For this cohort of patients, obinutuzumab with chlorambucil (O-Clb) was an international standard of care.[8] NICE also recommends VenO and acalabrutinib monotherapy as an option for those without TP53 disruption. For the high-risk group of patients with del17p/TP53 mutation, NICE-approved treatment options include idelalisib plus rituximab (Id + R), ibrutinib monotherapy, VenO, and acalabrutinib monotherapy. However, it was recognised in TA689 that Id+R is poorly tolerated and a less used option.[9]

Ibrutinib is an orally administered, small-molecule inhibitor of Bruton's tyrosine kinase (BTK), which is a type of targeted therapy that reduces abnormal B-cell proliferation and survival. Venetoclax is an orally administered, selective inhibitor of B-cell lymphoma-2 (BCL-2), an anti-apoptotic protein frequently overexpressed in leukaemia. It is another type of targeted therapy that is designed to block the function of BCL-2, thereby restoring apoptosis of cancer cells.

Ibrutinib as monotherapy or in combination with rituximab or obinutuzumab has a marketing authorisation in the UK for treating adult patients with previously untreated CLL. Ibrutinib as monotherapy or in combination with BR has a marketing authorization in the UK for treating

adult patients with CLL who have received at least one prior therapy. The CS focuses on ibrutinib in combination with venetoclax for adult patients with previously untreated CLL.

Current treatments which are recommended by NICE for previously untreated CLL and the proposed place of ibrutinib + venetoclax in the treatment pathway is presented in Document B, Figure 4 of the CS and is reproduced below as Figure 1. The EAG agrees that the company's proposed pathway is representative of current clinical practice and the anticipated positioning of ibrutinib + venetoclax is within its licensed indication.



CLL = chronic lymphocytic leukaemia; del17p = 17p deletion; FCR = fludarabine plus cyclophosphamide and rituximab; TP53 = tumour protein 53

Figure 1 Clinical pathway of care for previously untreated CLL patients, with proposed positioning of I+V in red [Reproduced from Figure 1, Document A of the CS]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with untreated CLL	As per final scope	NA	The population described in the CS matches that described in the NICE final scope.
Intervention	I+V	As per final scope	NA	The intervention described in the CS matches that described in the NICE final scope. At the time of the CS, the application for a marketing authorisation extension of ibrutinib (IMBRUVICA®) was submitted to the European Medical Agency (EMA) in November 2021. A marketing authorisation application for the MHRA (Medicines and Healthcare product Regulatory Agency) was to be submitted using the [redacted] in [redacted] at the time of the CS. Following the preparation of the CS, CHMP (Committee for Medicinal Products Human Use) of the EMA issued a positive opinion on 23 June 2022 for ibrutinib in combination with venetoclax (I+V) for adult patients with previously untreated CLL. The European Commission marketing authorisation approval for this indication was granted on 2nd August 2022. The final European Public Assessment Report (EPAR) was published on 22 September 2022.[10]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Comparator(s)	For people without del17p or TP53 mutation: • FCR • BR, for people for whom fludarabine-based therapy is unsuitable • O-Clb, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable • acalabrutinib, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable • VenO, for people for whom fludarabine-based or bendamustine-based therapy is unsuitable	For people with no del17p mutation, for whom fludarabine-based therapy is suitable (i.e., FCR-suitable population): • FCR For people with no del17p mutation, for whom fludarabine-based therapy is unsuitable (i.e., FCR-unsuitable population): • O-Clb • VenO • acalabrutinib For people with del17p/TP53 mutation (i.e., high-risk population): • VenO • acalabrutinib • ibrutinib alone, for people for	BR has been excluded as a relevant comparator for patients without a del17p/TP53 mutation, because it is rarely used in clinical practice and no longer recommended in the 2022 BSH guidelines.[8] This was validated at an advisory board of clinical and health economic experts conducted in March 2022[11] and was an assumption accepted by NICE in TA663.[12] Idelalisib with rituximab has been excluded as a relevant comparator for patients with a del17p/TP53 mutation because it is rarely used in clinical practice and clinical experts agree that it has now been superseded by ibrutinib and acalabrutinib due to the higher risk of infection and death. This was an approach accepted by NICE in the acalabrutinib (TA689)[9] and VenO appraisals (TA663)[12] and validated by	The EAG agrees that the company's choice of comparators is appropriate for this appraisal for the reasons specified by the company. For the FCR-suitable population, the CAPTIVATE trial in the CS provides single-cohort evidence for an oral fixed duration (FD) I+V combination. Comparative effectiveness with FCR was assessed using an indirect treatment comparison (ITC). The CAPTIVATE protocol specified inclusion of at least 125 participants without del17p in the FD cohort. A total of 17.0% of participants were with del17p or TP53 mutation. For the FCR-unsuitable population, the GLOW trial in the CS assessed the clinical effectiveness of I+V versus O-Clb. The EAG's clinical expert notes that the comparator in the trial (O-Clb) was standard of care when the trial started but that there is now a more effective treatment. Currently, these patients would receive one of obinutuzumab + venetoclax (VenO) or single agent acalabrutinib. The CS provided two separate anchored matching-adjusted indirect comparisons (MAIC) to assess the comparison with VenO, and with acalabrutinib, respectively. Eligibility criteria for GLOW specified "presence of del17p or known TP53 mutation" as an exclusion criterion. Participants were not screened for TP53 until after randomisation and a total of 4.3% of participants had

	For people with del17p or TP53 mutation: • acalabrutinib • VenO • ibrutinib alone, for people for whom CIT is unsuitable • idelalisib with rituximab	whom CIT is unsuitable	clinical expert opinion in May 2022.[13]	TP53 mutation. The EAG's clinical expert notes that screening for TP53 mutation is standard practice before initiating each line of treatment. For the population with del17p/TP53 mutation (i.e. high-risk population), there is a general paucity of evidence. The company thus made two assumptions: firstly, that ibrutinib efficacy was 'equivalent to acalabrutinib in the high risk population, based on the assumption made and accepted in TA689' (Document B of the CS, page 79);[9] and secondly that, overall, 'the clinical efficacy of I+V in high-risk patients was […] equivalent to FCR-unsuitable patients' (Document B of the CS, page 101 and Document A, page 17). The EAG's clinical expert considers that the first assumption (ibrutinib / acalabrutinib equivalence) is generally accepted and has been shown in a RCT. The EAG's clinical expert, however, questions the second assumption. While this assumption has been previously accepted, data from previous trials, e.g., RESONATE,[14] CLL-14,[15-17] and MURANO,[18] show that del17p/TP53 mutation still leads to a worse outcome even with these newer agents (ibrutinib or venetoclax used as a single agent), whether the combination of I+V overcomes this is yet to be elucidated.
Outcomes	The outcome measures to be considered include:	As per final scope	NA	The outcomes described in the CS match those described in the NICE final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• OS • PFS • response rates (including CR) • MRD • adverse effects of treatment • HRQoL			

Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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 PSS perspective. The availability and cost of biosimilar and generic products should be considered. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment	As per final scope and reference case	NA	The company's economic analysis aligns with the reference case. See Chapter 4 for a detailed critique.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	technologies will be considered.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people with del17p/TP53 mutation • according to IGHV mutation status (mutated or unmutated) • people for whom fludarabine-based therapy is unsuitable • people for whom bendamustine-based therapy is unsuitable	The submission addresses the following three populations: • people for whom fludarabine-based therapy is suitable • people for whom fludarabine-based therapy is unsuitable • people with del17p/TP53 mutation	IGHV test results are not required by NICE or CDF criteria to receive a specific treatment in first-line CLL and ibrutinib is efficacious independent of IGHV status;[19] therefore, the results in the FCR-suitable and FCR-unsuitable populations are more representative of UK clinical practice than in populations determined by IGHV mutation status. Patients from GLOW have co-morbidities which would make them unsuitable for treatment with FCR or BR – given that BR is not routinely used in clinical practice, a BR-unsuitable subgroup was not incorporated in the model. However, the results for the FCR-unsuitable population are generalisable to a BR-unsuitable population.	The EAG agrees with the company's position.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Special considerations including issues related to equity or equality	None	There is an urgent need for access to novel treatments for younger, fitter patients with CLL as currently only FCR or VenO via the CDF are available to them, with no access to a fully oral treatment. I+V will address this inequality.		The EAG agrees with the company's position.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The EAG'S appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 EAG's appraisal of the systematic review methods presented in the CS

Review process EAG	EAG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, PubMed/Medline, and CENTRAL, for primary and secondary research. Relevant conference proceedings were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	PARTLY	Appendix D, sectionD.1.4: "*abstracts were screened by two independent investigators using the pre-specified inclusion and exclusion criteria*" and "*full-text articles were reviewed by a single investigator, and all articles that were rejected at this screening level were independently verified by a*

		second investigator, with regards to the accuracy of and reason for the rejection". The EAG considers this strategy to be appropriate
Was data extraction conducted by two or more reviewers independently?	No	From clarification response: "*data was first extracted independently into a data extraction form by one investigator, and the accuracy and completeness of the extracted data was subsequently validated by a second investigator*". The EAG considers this to be an appropriate strategy
Were appropriate criteria used to assess the risk of bias of identified studies?	PARTLY	Appendix D, section D.2.3: "*quality assessment using a tool based on the NICE-specified summary tables was conducted*". Document B, Table 14 also reported assessment using the CRD's guidance. Criteria in both these assessments are appropriate for assessment of RCTs (and, thus, GLOW) but largely not relevant to a single-arm study such as the CAPTIVATE FD cohort
Was the risk of bias assessment conducted by two or more reviewers independently?	No	From clarification response: "*Quality assessment was independently carried out by one investigator and information was validated by a second investigator*". The EAG is of the opinion that this strategy is acceptable
Was identified evidence synthesised using appropriate methods?	Yes	The general approach to the evidence synthesis was appropriate though there are issues around the degree of uncertainty around the results.

The EAG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5. *The EAG considers the methods used by the company for the systematic review of clinical effectiveness evidence adequate.*

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	YES
2. Is there evidence of a substantial effort to search for all of the relevant research?	YES
3. Is the validity of included studies adequately assessed?	YES
4. Are sufficient details of the individual studies presented?	YES
5. Are the primary studies summarised appropriately?	YES

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Document B, Section B.2 of the CS. The company presents clinical effectiveness evidence from two studies:

- CAPTIVATE: an international, multi-centre, phase II trial consisting of two cohorts: the fixed duration (FD) cohort (the focus of the CS; referred to as CAPTIVATE hereafter) and the minimal residual disease (MRD) cohort. CAPTIVATE FD is an open-label, single arm cohort, enrolled sequentially after the MRD cohort
- GLOW: an international, multi-centre, open label, phase III RCT.

An overview of the two studies is presented in Document B, Table 8 of the CS and reproduced as Table 6.

Table 6 Clinical effectiveness evidence [reproduced from Table 8, Document B of the CS]

Study	CAPTIVATE	GLOW
Study design	International, multi-centre, phase II, 2-cohort clinical trial, including the FD cohort (the focus of this submission for CAPTIVATE) and the MRD cohort	International, multi-centre, open-label, phase III randomised clinical trial

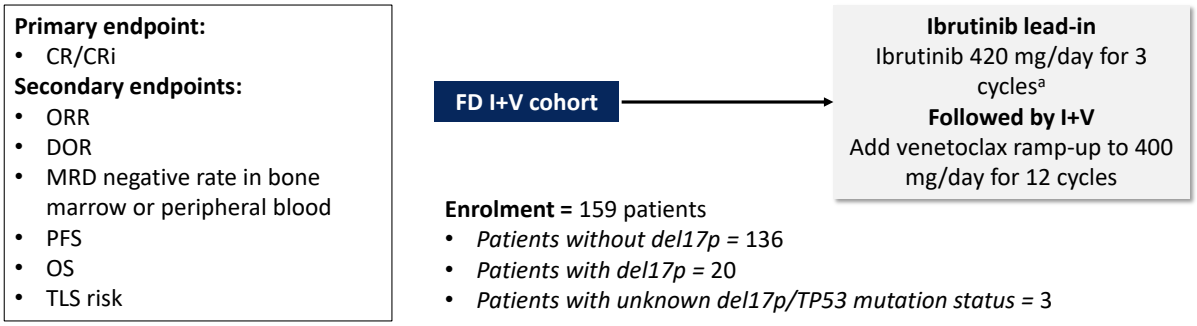
Study	CAPTIVATE		GLOW	
Population	FD cohort: • Age ≥18 and ≤70 years • Diagnosis of CLL/SLL meeting iwCLL criteria • Active disease requiring treatment per iwCLL criteria • Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm by longest diameter • ECOG PS ≤2 • No prior therapy for CLL or SLL • No suspected Richter's syndrome		• Age ≥65 years, **or** 18 to 64 years of age with CIRS score >6 and/or CrCl <70 mL/min • Diagnosis of CLL/SLL meeting iwCLL criteria • Active disease requiring treatment per iwCLL criteria • Measurable nodal disease by CT defined as ≥1 lymph node >1.5 cm by longest diameter • ECOG PS ≤2 • No prior anti-leukaemic therapy for CLL or SLL • No del17p or known TP53 mutation • No CNS involvement or suspected Richter's syndrome	
Intervention(s)	I+V		I+V	
Comparator(s)	None		O-Clb	
Study supports application for marketing authorisation?	Yes	✓	Yes	✓
Study used in the economic model?	Yes	✓[a]	Yes	✓
Rationale if study not used in the model	Not applicable		Not applicable	
Reported outcomes specified in the decision problem[b]	• **PFS** • **OS** • **AEs**		• **PFS** • **OS** • **AEs** • **HRQoL**	
All other reported outcomes	• MRD negative rate • CR/CRi rate • ORR • Rate of sustained haematological improvement • DOR • Reduction of TLS risk • Response to ibrutinib reintroduction following disease progression		• MRD negative rate • CR/CRi rate • ORR • Rate of sustained haematological improvement • Time to first meaningful improvement in FACIT-Fatigue score • DOR • Reduction of TLS risk	

AE = adverse event; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukaemia; CNS = central nervous system; CR = complete response; CrCl = creatinine clearance; CRi = complete response with incomplete bone marrow recovery; CT = computerised tomography; del17p = 17p deletion; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FD = fixed duration; FISH = fluorescent in situ hybridisation; O-Clb = obinutuzumab + chlorambucil; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; SLL = small lymphocytic lymphoma; TLS = tumour lysis syndrome; TP53 = tumour protein 53

[a] Only the FD cohort is used in the economic model.

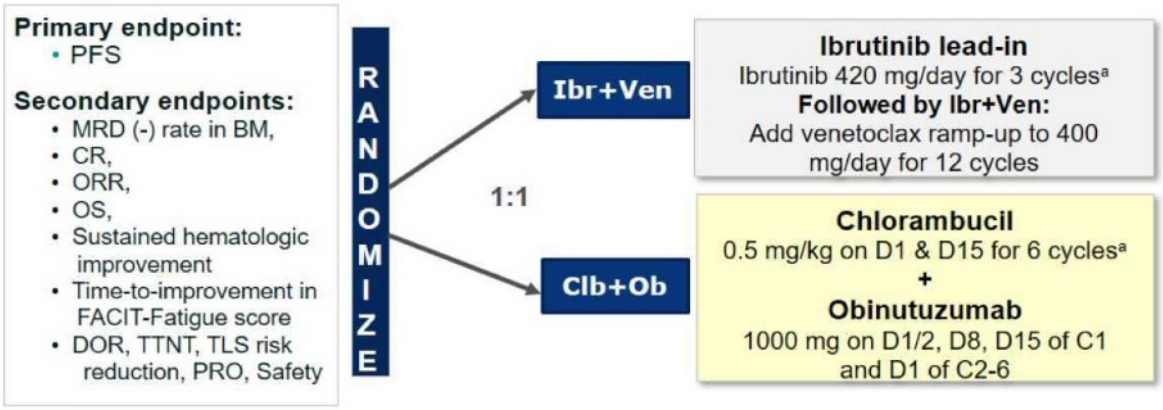
[b] Outcomes that are incorporated into the model are bolded. Note that OS is not directly used in the model, but is used for validation.

The methods of the two studies are reported in Document B, Section 2.3 of the CS and summarised in Document B, Table 9 of the CS. The primary objective of CAPTIVATE was to evaluate the depth of response with I+V administered for a fixed duration by assessment of complete response (CR/CR with incomplete bone marrow recovery [CRi]) in people with previously untreated CLL or SLL. The primary objective of GLOW was to compare PFS from treatment with I+V to treatment with O-Clb in people who were not suitable for FCR. Key eligibility criteria for CAPTIVATE and GLOW are reported in Document B, Table 9 of the CS. The main difference between the populations of the trials was the suitability of participants for FCR; in CAPTIVATE, participants were between 18 and 70 years of age whereas in GLOW, participants were at least 65 years old or aged 18 to 64 with CIRS score >6 and/or CrCl <70mL/min. In addition, GLOW inclusion criteria specified no del17p or known TP53 mutation. The study designs of CAPTIVATE FD and GLOW are reported in Document B, Figure 3 and Figure 4 of the CS, respectively and reproduced as Figure 2 and Figure 3 below.



CR = complete response; CRi = complete response with incomplete bone marrow recovery; del17p = 17p deletion; DOR = duration of response; FD = fixed duration; I+V = ibrutinib + venetoclax; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TLS = tumour lysis syndrome
a One cycle = 28 days
Source: Pharmacyclics [Data on File], 2019[20]

Figure 2 Trial design (CAPTIVATE FD cohort) [reproduced from Figure 3, Document B of the CS]



Enrolment = 211 patients
- *Patients randomised to Ibr+Ven* = 106
- *Patients randomised to O-Clb* = 105

Stratification:
- IGHV status (mutated vs. unmutated vs. not available)
- Del11q (yes vs. no)

BM = bone marrow; C = cycle; Clb+Ob = chlorambucil + obinutuzumab; CR = complete response; D = day; del11q = 11q deletion; DOR = duration of response; Ibr+Ven = ibrutinib + venetoclax; IGHV = immunoglobulin heavy chain variable region; MRD = minimal residual disease; O-Clb = obinutuzumab + chlorambucil; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; TLS = tumour lysis syndrome; TTNT = time to next treatment
[a] One cycle = 28 days

Source: Janssen Research & Development LLC [Data on File], 2021[21]

Figure 3 Trial design (GLOW) [reproduced from Figure 4, Document B of the CS]

CAPTIVATE was conducted in 39 centres in five countries in Europe (23.3%; there were no centres in the UK), North America (45.9%) and Asia-Pacific region (30.8%). GLOW was conducted in 67 centres in 14 countries in Europe and North America, including [redacted] participants ([redacted] in the I+V group, [redacted] in the O-Clb group) across seven centres in the UK. Participant flows of CAPTIVATE FD and GLOW are presented in Appendix D, Sections D.2.1 and D.2.2, respectively. In CAPTIVATE FD, 147/159 (92.5%) of participants completed planned ibrutinib treatment and 149/159 (93.7%) completed planned venetoclax treatment; 12/159 (7.5%) discontinued ibrutinib treatment early, 4/159 (2.5%) discontinued venetoclax treatment early and 6/159 (3.8%) received ibrutinib but not venetoclax. The EAG's clinical expert is uncertain as to why participants would receive ibrutinib but not venetoclax but notes that receiving only ibrutinib would reduce effectiveness. At the data cut-off for the primary analysis, [redacted] of participants continued to be followed (median time on study 27.9 months) and [redacted] were still being followed at the cut-off for extended follow-up (median time on study 38.7 months). In GLOW, a total of 211 participants were randomised (I+V, n=106; O-Clb, n=105), of which 24/106 (22.6%) had discontinued I+V treatment and 5/105 (4.8%) had discontinued O-Clb treatment at the data

cut-off for the primary analysis; 11/106 (10.4%) participants in the I+V group and 11/105 (10.5%) of the O-Clb group had died but were considered to have completed study participation. Median duration of treatment was 13.8 months and 5.1 months, respectively. At the cut-off for extended follow-up, [redacted] participants in the I+V group and [redacted] participants in the O-Clb were still being followed; at this point, [redacted] participants in the I+V group and [redacted] participants in the O-Clb group had died. The EAG's clinical expert notes that the larger proportion of participants discontinuing in the I+V arm is likely due to the longer duration of treatment as compared to the O-Clb arm and is not concerned with the difference in rates of discontinuation.

Quality appraisal of the CAPTIVATE FD cohort was based on the NICE-specified summary tables and the CRD's guidance, of which the criteria were largely relevant to RCTs rather than non-randomised studies. The EAG, therefore, conducted an informal assessment of the CAPTIVATE FD cohort based on a checklist adapted from several sources which was developed by the HSRU, University of Aberdeen, in partnership with the NICE Review Body for Interventional Procedures (ReBIP).[22-25] In the opinion of the EAG, the CAPTIVATE FD cohort involves a representative sample from a relevant population with participants at a similar point in severity of disease. The study involved a clearly defined intervention undertaken by appropriate staff and in an appropriate setting. Data were collected prospectively, and appropriate outcomes and measures were used. Information on participant flow was fully reported and all participants were accounted for. Prognostic factors such as relevant cytogenetic factors were identified. Overall, the EAG considers the CAPTIVATE FD cohort to be of acceptable quality but subject to the bias inherent in studies of this design.

Appendix D, section D.2.3 of the CS reported that GLOW was an open-label study and assessed the risk of bias of the study as "moderate" as "patients, providers and assessors were not blinded". In contrast, Document B, Table 14 reports a response of 'Yes' to the question 'Were the care providers, participants and outcome assessors blind to treatment allocation'. GLOW was, in fact, an open-label study, however, the independent review committee (IRC) who performed tumour assessment were required to be blinded to study treatment group assignment.

CAPTIVATE was funded by Pharmacyclics LLC. GLOW was funded by Janssen Research & Development, LLC and Pharmacyclics. In general, the EAG agrees with the company's

assertion that CAPTIVATE and GLOW are high quality trials, with the caveats of non-randomised studies and funding by the pharmaceutical industry.
Details of the baseline characteristics of CAPTIVATE FD and GLOW are reported as Document B, Table 10 and Table 11 of the CS and reproduced as Table 7 and Table 8, respectively, below.

In the CAPTIVATE FD total sample of 159 participants, 20 had del17p and 3 participants had an unknown del17p/TP53 mutation status, leaving 136 participants in the non-del17p cohort. Of these 136 participants, 7 had TP53 mutation. Despite the NICE final scope specifying either people with or without del17p or TP53 mutation, the CAPTIVATE trial eligibility criteria do not mirror this specification. The EAG's clinical expert notes that people with CLL in clinical practice are routinely screened for TP53 mutation before each line of treatment. The mean age of participants in CAPTIVATE FD without del17p was 57.9 years with around three-quarters aged < 65 years. Around two-thirds of the participants were male. Most participants were classified as Rai Stage 0/I/II (indicating less advanced disease) or ECOG 0 (indicating fully active). Almost one-fifth of participants had del11q and more than half had unmutated IGHV, the latter two factors indicating high-risk disease, albeit the EAG's clinical expert is of the opinion that del17p/TP53 mutation is the most important risk factor in clinical practice.

In GLOW, a total of nine participants (4.3%) had TP53 mutation, reflecting the exclusion criterion of "known TP53 mutation" and the fact that participants were not screened until after enrolment in the trail and subsequent randomisation. Of these nine participants, seven were in the I+V group (6.6%) and two in the O-Clb group (1.9%). The CS notes that TP53 mutation is a strong negative prognostic factor for O-Clb but that the small proportion of participants with the mutation should have minimal impact on the results. The EAG clinical expert notes that there is limited published data on I+V in TP53 mutated disease but that TP53 mutation is a negative prognostic factor for each drug individually and likely to remain a negative factor in the combination. However, the magnitude of the effect is much smaller than with O-Clb. Thus, the EAG agrees that the small proportion of participants with TP53 mutation in both groups is unlikely to impact upon the outcomes of the study. The mean age of participants overall was 71.5 years, with around one-third aged from 70 to <74 years and a further third aged over 75 years. More than half of participants were male. Around half were

classified as Binet stage B and slightly less than half Binet stage C (indicating advanced disease).

Table 7 Characteristics of participants in CAPTIVATE FD (all treated population) and GLOW (ITT population)[adapted from Tables 10 and 11, Document B of the CS]

Baseline characteristic[a]	CAPTIVATE FD		GLOW	
	Non-del17p	All treated	I+V	O-Clb
Patients, n	**n=136**	**n=159**	**n=106**	**n=105**
Age				
Median years (range)	59.5 (33, 71)	60.0 (33, 71)	71.0 (47, 93)	71.0 (57, 88)
Mean years (SD)	57.9 (8.68)	58.0 (8.51)	71.0 (8.02)	72.0 (6.16)
<65 years, n (%)	97 (71.3)	114 (71.7)	16 (15.1)	11 (10.5)
≥65 years, n (%)	39 (28.7)	45 (28.3)	NR	NR
≥65 to <70 years, n (%)	NR	NR	23 (21.7)	27 (25.7)
≥70 to <74 years, n (%)	NR	NR	32 (30.2)	30 (28.6)
≥75, n (%)	NR	NR	35 (33.0)	37 (35.2)
Sex (%)				
Male, n (%)	88 (64.7)	106 (66.7)	59 (55.7)	63 (60.0)
Race, n (%)				
Asian	3 (2.2)	3 (1.9)	0 (0.0)	1 (1.0)
Black or African American	1 (0.7)	1 (0.6)	NR	NR
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (0.6)	NR	NR
White	124 (91.2)	147 (92.5)	101 (95.3)	101 (96.2)
Multiple	NR	NR	1 (0.9)	0 (0.0)
Not reported	7 (5.1)	7 (4.4)	4 (3.8)	3 (2.9)
Ethnicity, n (%)				
Hispanic or Latino	3 (2.2)	5 (3.1)	1 (0.9)	3 (2.9)
Not Hispanic or Latino	128 (94.1)	149 (93.7)	101 (95.3)	99 (94.3)
Not reported	5 (3.7)	5 (3.1)	4 (3.8)	3 (2.9)
Diagnosis, n (%)				
CLL	125 (91.9)	146 (91.8)	96 (90.6)	101 (96.2)
SLL	11 (8.1)	13 (8.2)	10 (9.4)	4 (3.8)
Time from initial diagnosis to randomisation in months				
Median (range)	37.4 (1, 284)	33.8 (1, 284)	35.8 (0.5, 227.8)	35.4 (0.7, 178.8)

Baseline characteristic[a]	CAPTIVATE FD		GLOW	
	Non-del17p	All treated	I+V	O-Clb
Patients, n	**n=136**	**n=159**	**n=106**	**n=105**
Rai stage (CLL only)				
Stage 0/I/II, n (%)	100 (73.5)	113 (71.1)	41/96 (42.7)	48/101 (47.5)
Stage III/IV, n (%)	34 (25.0)	44 (27.7)	55/96 (57.3)	53/101 (52.5)
Missing	2 (1.5)	2 (1.3)	0 (0.0)	0 (0.0)
Binet stage (CLL only)				
N	NR	NR	96	101
Binet stage A, n (%)	NR	NR	7 (7.3)	8 (7.9)
Binet stage B, n (%)	NR	NR	46 (47.9)	53 (52.5)
Binet stage C, n (%)	NR	NR	43 (44.8)	40 (39.6)
ECOG PS, n (%)				
0	97 (71.3)	110 (69.2)	35 (33.0)	39 (37.1)
1	39 (28.7)	49 (30.8)	58 (54.7)	54 (51.4)
1-2	0 (0.0)	0 (0.0)	71 (67.0)	66 (62.9)
CIRS total score, n (%)				
≤6	NR	NR	32 (30.2)	44 (41.9)
>6	NR	NR	74 (69.8)	61 (58.1)
Bulky disease[b]				
≥5 cm, n (%)	44 (32.4)	48 (30.2)	41 (39.0)	38 (36.2)
≥10 cm, n (%)	5 (3.7)	5 (3.1)	0 (0.0)	4 (3.8%)
Cytopenia, n (%)[c]				
Haemoglobin ≤110 g/L	30 (22.1)	37 (23.3)	NR	NR
Platelets ≤100 x 10^9 /L	18 (13.2)	21 (13.2)	NR	NR
Absolute neutrophil count ≤1.5 x 10^9 /L	13 (9.6)	13 (8.2)	NR	NR
Any of the above	45 (33.1)	54 (34.0)	NR	NR
Yes	NR	NR	58 (54.7)	65 (61.9)
del17p or TP53 mutation, n (%)				
Yes	7 (5.1)	27 (17.0)	7 (6.6)	2 (1.9)
No	129 (94.9)	129 (81.1)	99 (93.4)	103 (98.1)
Unknown	0	3 (1.9)	0 (0.0)	0 (0.0)
TP53 mutation, n (%)				

Baseline characteristic[a]	CAPTIVATE FD		GLOW	
	Non-del17p	All treated	I+V	O-Clb
Patients, n	**n=136**	**n=159**	**n=106**	**n=105**
Yes	7 (5.1)	16 (10.1)	7 (6.6)	2 (1.9)
No	129 (94.9)	142 (89.3)	99 (93.4)	103 (98.1)
Unknown	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
del17p, n (%)				
Yes	0 (0.0)	20 (12.6)	0 (0.0)	0 (0.0)
del11q, n (%)				
Yes	28 (20.6)	28 (17.6)	20 (18.9)	18 (17.1)
IGHV, n (%)				
Mutated	55 (40.4)	66 (41.5)	27 (25.5)	27 (25.7)
Unmutated	78 (57.4)	89 (56.0)	55 (51.9)	54 (51.4)
Unknown	3 (2.2)	4 (2.5)	24 (22.6)	24 (22.9)
High-risk population[d], n (%)				
Yes	NR	NR	63 (59.4)	60 (57.1)
Elevated LDH, n (%)				
Yes (>ULN)	NR	NR	35 (33.0)	51 (48.6)

CLL = chronic lymphocytic leukaemia; del11q = 11q deletion; del17p = 17p deletion; ECOG = Eastern Cooperative Oncology Group; IGHV = immunoglobulin heavy chain variable region; INV = investigator; SLL = small lymphocytic lymphoma; TP53 = tumour protein p53

[a] Baseline is defined as the last measurement taken on or prior to the first dose date of study treatment. [b] Bulky disease is based on the largest longest diameter of the target lymph node at screening per INV assessment. Source: Pharmacyclics [Data on File], 2021; Wierda, 2022

[c] Cytopenia was defined as one of the following: haemoglobin ≤110 g/dL, platelet counts ≤100 x 10^9/L or ANC ≤1.5 x 10^9/L.

[d] High-risk population was defined as the presence of any one of the following: TP53 mutation, del11q or unmutated IGHV.

Sources: Janssen Research & Development LLC [Data on File], 2021;[21] Kater, 2022;[26] Clinicaltrials.gov, 2022[27]

One-third of participants were scored as 0 for ECOG and two-thirds as ECOG 1-2 (indicating restrictions in performance). Thirty-eight participants (18.0%) had del11q and 109 (51.7%) unmutated IGHV, with over half of the participants across both groups (58.3%) described as high-risk. Overall, characteristics were balanced between the groups except for CIRS total score (>6: 69.8% in the I+V group and 58.1% in the O-Clb group) and elevated LHD (33.0% and 48.6%, respectively). The EAG's clinical expert notes that CIRS score>6 is predictive of a worse outcome, thus poorer outcomes would be expected in the I+V group due to a higher proportion of scores >6. On the other hand, LDH is not predictive of outcome and is not considered important in this context.

In general, the EAG's clinical expert is satisfied that the baseline characteristics of CAPTIVATE FD and GLOW are representative of patients with untreated CLL seen in clinical practice in the UK.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: overall survival (OS), progression-free survival (PFS), response rates (including complete response [CR]), minimal residual disease (MRD), adverse effects and health-related quality of life (HRQoL).

In CAPTIVATE FD, the all-treated population (i.e., all 159 participants who received at least one dose of study treatment) was used for efficacy and safety analyses. Primary analysis was based on data cut-off date 12th November 2020, with a median of 27.9 months follow-up. Further analysis was based on data cut-off of 4th August 2021, for a total of 38.7 months follow-up, including 136 participants without del17p. Outcomes reported at the extended follow-up were used by the company to inform the indirect treatment comparisons and economic analysis. Thus, the focus of this section will be outcomes the extended analysis followed by a summary of the primary analysis, for completeness.

Primary endpoints: CAPTIVATE FD [extended follow-up]

The primary outcome of CAPTIVATE FD was depth of response by assessment of CR (i.e. best overall response of CR/CR with incomplete bone marrow [BM] recovery [CRi] per investigator assessment). At extended follow-up, the CR/CRi rate for participants without del17p (n=136) was 58.1% (95%CI 49.8, 66.4) as assessed by investigator and 64.0% (95%CI 55.9, 72.0) as assessed by independent review committee (IRC). These rates were

comparable to the all-treated population (n=159), which were 57.2% (95%CI 49.5, 64.9) and 62.3% (95%CI 54.7, 69.8), respectively. Durable responses (defined as duration of CR/CRi for 12 months based on investigator assessment) at the extended follow-up were observed in 73/79 (92.4%) of the non-del17p population achieving CR/CRi (73/136 [53.7%] of all patients) and 85/91 (93.4%) of the all-treated population who achieved CR/CRi (85/159 [53.5%] of all patients). Similar rates of durable responses at extended follow-up were also observed with IRC assessment for those who had achieved CR/CRi (90.8% and 90.9%, respectively) and among all patients (58.1% and 56.6%, respectively).

Secondary endpoints: CAPTIVATE FD [extended follow-up]

Secondary endpoints used in the economic model were progression-free survival (PFS) and overall survival (OS).

- **PFS** (time from date of first study treatment to date of progressive disease per investigator assessment or date of death, whichever occurred first): At extended follow-up, median investigator assessed PFS was not reached for patients in the all-treated population or for patients without del17p. A Kaplan-Meier plots is presented by the company in Document B, Figure 7 of the CS, reproduced as Figure 4 below. At 36 months, Kaplan-Meier point estimates were 89.1% (95%CI 82.3, 93.4) for patients without del17p, 88.1% (95%CI 81.7, 92.3) for the all-treated population and 79.9% (95%CI 58.3, 91.1) for people with del17p/TP53 mutation. Median PFS by IRC assessment was [redacted] with [redacted] for patients without del17p and [redacted] for all patients.

del17p = 17p deletion; FD = fixed duration; INV = investigator; KM = Kaplan-Meier; PFS = progression-free survival
Source: CAPTIVATE IPD

Figure 4 KM plot of INV-assessed PFS (CAPTIVATE; all treated and no-del17p populations extended follow-up) [reproduced from Figure 7, Document B of the CS]

- **OS** (from the date of first study treatment dose to death from any cause): Median OS was not reached for the all-treated population or the non-del17p population at extended follow-up. There were no additional deaths over and above the three deaths in the non-del17p population reported at the time of the primary analysis (two due to cardiac events and one due to intracranial haemorrhage). Kaplan-Meier point estimates were 97.7% (95%CI) in the non-del17p population and 98.1% (95%CI 94.2, 99.4) for all patients. The Kaplan-Meier plot of OS at extended follow-up is reported in Document B, Figure 10 of the CS and reproduced as Figure 5 below.

CI = confidence interval; del17p = 17p deletion; FD = fixed duration; KM = Kaplan-Meier; OS = overall survival
Source: CAPTIVATE IPD

Figure 5 KM plot of OS (CAPTIVATE; all treated and no-del17p populations extended follow-up) [reproduced from Figure 10, Document B of the CS]

The CS presents a summary of clinical effectiveness outcomes at extended follow-up for non-del17p and all-treated populations in Document B, Table 15, reproduced as Table 8 below.

Summary of clinical effectiveness: CAPTIVATE FD [primary analysis]

A summary of clinical effectiveness at the time of the primary analysis (median 27.9 months follow-up) is presented in Appendix M, Table 98 of the company submission, reproduced as Table 9 below.

Table 8 Summary of clinical effectiveness at a median follow-up of 38.7 months (CAPTIVATE FD cohort; extended follow-up analysis) [reproduced from Table 15, Document B of the CS]

Endpoint	Assessment	Outcome	I+V, without del17p (n=136)	I+V, all treated (N=159)
Primary Endpoint				
Depth of response per CR/CRi	INV	Rate, % (95% CI)	58.1 (49.8, 66.4)	57.2 (49.5, 64.9)
	IRC	Rate, % (95% CI)	64.0 (55.9, 72.0)	62.3 (54.7, 69.8)
Secondary Endpoints				
ORR	INV	Rate, % (95% CI)	95.6 (92.1, 99.0)	96.2 (92.3, 99.2)
	IRC	Rate, % (95% CI)	[redacted]	[redacted]
DOR	INV	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
		Rate at [redacted] months, % (95% CI)	89.8 (83.0, 93.9)	88.6 (82.3, 92.7)
	IRC	Median, months (95% CI)	[redacted]	[redacted]
		Rate at [redacted] months, % (95% CI)	[redacted]	[redacted]
MRD negative rate by flow cytometry	BM	Rate, % (95% CI)	61.8 (53.6, 69.9)	59.7 (52.1, 67.4)
	PB	Rate, % (95% CI)	76.5 (69.3, 83.6)	76.7 (70.2, 83.3)
PFS	INV	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
		Rate at 36 months, % (95% CI)	89.1 (82.3, 93.4)	88.1 (81.7, 92.3)
	IRC	Median, months (95% CI)	[redacted]	[redacted]
		Rate at [redacted] months, % (95% CI)	[redacted]	[redacted]
OS	Not applicable	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
		Rate at [redacted] months, % (95% CI)	97.7 (93.2, 99.3)	98.1 (94.2, 99.4)
Reduction of TLS risk	Not applicable	Proportion with high risk of TLS at baseline reduced to medium/low,[b] %	Not reported	94.1[c]

BM = bone marrow; CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; DOR = duration of response; I+V = ibrutinib + venetoclax; INV = investigator; IRC = Independent Review Committee; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; OS = overall survival; PB = peripheral blood; PFS = progression-free survival; TLS = tumour lysis syndrome

[a] [redacted] [b] After three cycles of ibrutinib monotherapy

[c] Results are presented based on the primary analysis; no analysis on reduction of TLS risk was conducted during extended follow-up

Source: Pharmacyclics [Data on File], 2021[28]

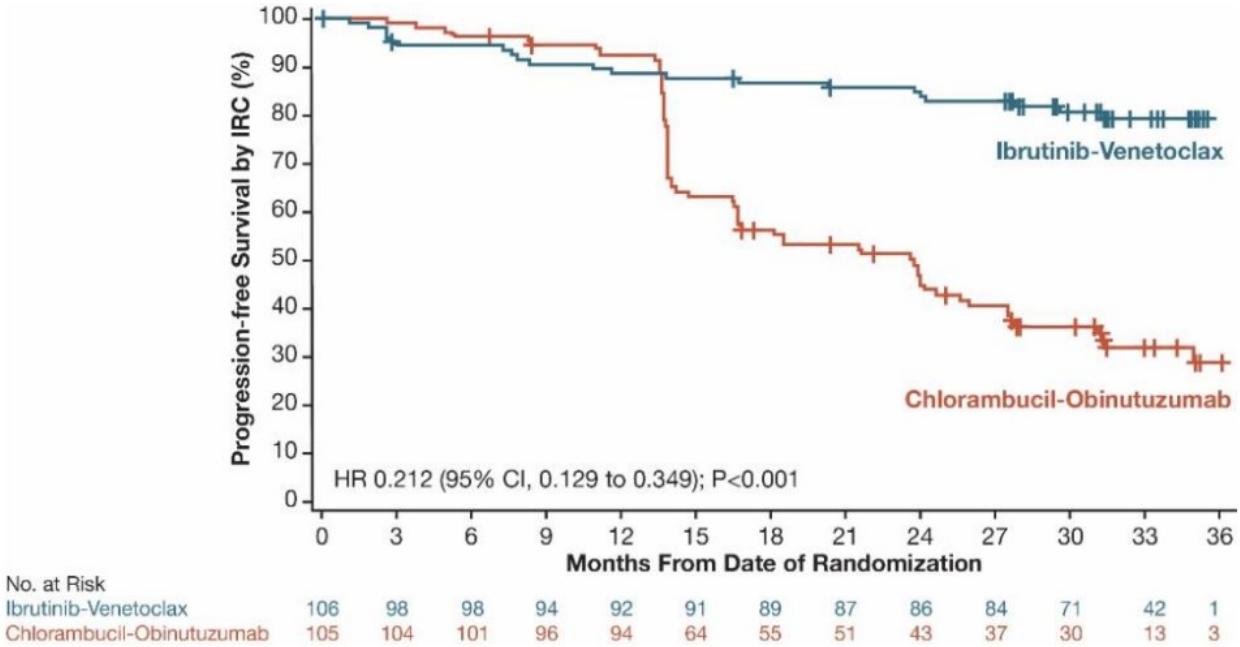
Table 9 Summary of clinical effectiveness at a median follow-up of 27.9 months (CAPTIVATE FD Cohort; primary analysis) [reproduced from Table 98, Appendix M of the CS]

Endpoint	Assessment	Outcome	I+V, without del17p (n=136)	I+V, all treated (N=159)
Primary Endpoint				
Depth of response per CR/CRi	INV	Rate, % (95% CI)	55.9 (47.5, 64.2)	55.3 (47.6, 63.1)
	IRC	Rate, % (95% CI)	61.0 (52.8, 69.2)	59.7 (52.1, 67.4)
Secondary Endpoints				
ORR	INV	Rate, % (95% CI)	95.6 (92.1, 99.0)	96.2 (92.3, 99.2)
	IRC	Rate, % (95% CI)	[redacted]	[redacted]
DOR	INV	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
		Rate at 24 months, % (95% CI)	96.1 (90.8, 98.3)	94.7 (89.6, 97.3)
	IRC	Median, months (95% CI)	[redacted]	[redacted]
		Rate at 24 months, % (95% CI)	[redacted]	[redacted]
MRD negative rate by flow cytometry	Bone marrow	Rate, % (95% CI)	61.8 (53.6, 69.9)	59.7 (52.1, 67.4)
	Peripheral blood	Rate, % (95% CI)	76.5 (69.3, 83.6)	76.7 (70.2, 83.3)
PFS	INV	Median, months (95% CI)	NE [redacted]	NE [redacted]
		Rate at 24 months, % (95% CI)	96.2 (91.1, 98.4)	94.8 (89.8, 97.3)
	IRC	Median, months (95% CI)	[redacted]	[redacted]
		Rate at 24 months, % (95% CI)	[redacted]	[redacted]
OS	Not applicable	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
		Rate at 24 months, % (95% CI)	97.7 (93.2, 99.3)	98.1 (94.2, 99.4)
Reduction of TLS risk	Not applicable	Proportion with high risk of TLS at baseline reduced to medium/low,[a] %	Not reported	94.1

CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; DOR = duration of response; I+V = ibrutinib + venetoclax; INV = investigator; IRC = Independent Review Committee; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TLS = tumour lysis syndrome; [a] After three cycles of ibrutinib monotherapy; Source: Pharmacyclics [Data on File], 2021;[28] Tam, 2022[29]

Primary endpoints: GLOW [extended follow-up]

In GLOW, the ITT population (i.e. all randomised participants; n=211) was used for all primary and secondary endpoints. Primary analysis was based on data cut-off date 26th February 2021, with a median of 27.7 months follow-up. Further analysis was based on data cut-off date 19th August 2021 with a median of 34.1 months follow-up. Outcomes reported at the extended follow-up were used by the company to inform the indirect treatment comparisons and economic analysis, thus will be the focus of this section. A summary of the primary analysis will then be presented, for completeness. The primary endpoint of GLOW was independent review committee (IRC)-assessed PFS (defined as the duration from randomisation to disease progression or death). At extended follow-up, there was a statistically significant improvement in PFS for participants in the I+V group as compared to the O-Clb group (HR 0.21; 95%CI 0.13, 0.35, nominal p<0.0001). Median PFS was not reached by the I+V group and was 23.7 months for the O-Clb group. Document B, Figure 12 of the CS presents the Kaplan-Meier plot of IRC-assessed PFS, reproduced ass Figure 6 below.



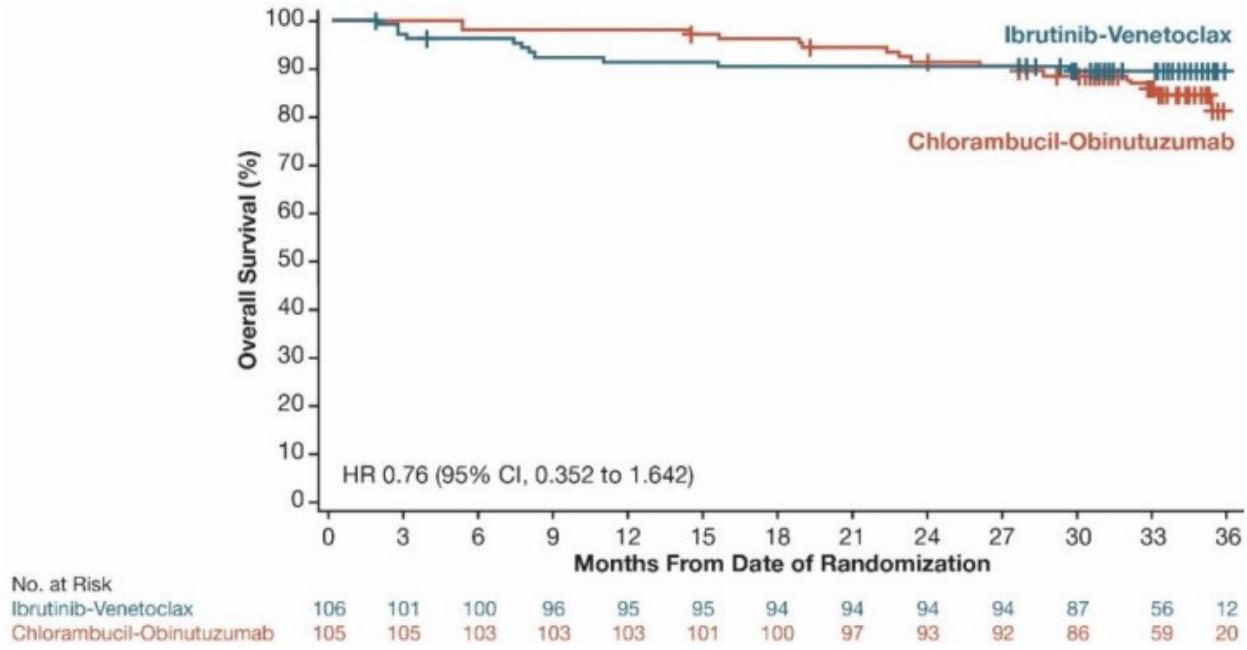
CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; ITT = intent-to-treat; KM = Kaplan-Meier; PFS = progression-free survival
Source: Kater, 2022[26]

Figure 6 KM plot of IRC-assessed PFS (GLOW; ITT extended follow-up analysis) [reproduced from Figure 12, Document B of the CS]

[redacted]

Secondary endpoints: GLOW [extended follow-up]

- **OS** (defined as OS from date of randomisation to death from any cause): At extended follow-up, median OS was not reached in either treatment group. There were four additional deaths in the O-Clb group and none in the I+V group, on top of the 11 deaths in the I+V group and 12 deaths in the O-Clb group reported at the time of the primary analysis (HR 0.76; 95%CI 0.35, 1.64, nominal p=0.4837). The Kaplan-Meier plot of OS at extended follow-up is presented in Document B, Figure 14 of the CS and reproduced as Figure 7 below.



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; KM = Kaplan-Meier; OS = overall survival
Source: Kater, 2022[26]

Figure 7 KM plot of OS (GLOW; ITT extended follow-up analysis) [reproduced from Figure 14, Document B of the CS]

The CS presents a summary of clinical effectiveness outcomes at extended follow-up for GLOW in Document B, Table 16, reproduced as Table 10 below.

Summary of clinical effectiveness: GLOW [primary analysis]

A summary of clinical effectiveness at the time of the primary analysis (median 27.7 months follow-up) is presented in Appendix M, Table 101 of the CS, reproduced as Table 11 below.

Table 10 Summary of clinical effectiveness at a median follow-up of 34.1 months (GLOW; ITT extended follow-up analysis) [reproduced from Table 16, Document B of the CS]

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
Primary Endpoints			
IRC-assessed PFS	Median, months (95% CI)	NE (NE, NE)	23.7 (16.6, 26.1)
	Rate at 30 months, % (95% CI)	80.5% (71.4, 86.9)	35.8% (26.4, 45.3)
	HR (95% CI; p-value)	0.21 (0.13, 0.35; nominal p<0.0001[a])	
INV-assessed PFS (supplementary analysis)	Median, months (95% CI)	[redacted]	[redacted]
	Rate at 30 months, % (95% CI)	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Key Secondary Endpoints Tested in a Hierarchical Manner			
MRD negative rate in BM by NGSb	Rate, % (95% CI)	55.7 (46.2, 65.1)	21.0 (13.2, 28.7)
	Rate ratio (95% CI; p-value)	2.65 (1.75, 3.99; p<0.0001[c])	
IRC-assessed CR (CR/CRi) rate	Rate, % (95% CI)	40.6 [redacted]	12.4 [redacted]
	Rate ratio (95% CI; p-value)	[redacted]	
IRC-assessed ORR	Rate, % (95% CI)	86.8 (80.3, 93.2)	[redacted]
	Rate ratio (95% CI, p-value)	1.02 (0.92, 1.14; p=0.6991[c])	
OS	Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
	Rate at 30 months, % (95% CI)	89.4 (81.7, 94.0)	[redacted]
	HR (95% CI, p-value)	0.76 (0.35, 1.64; nominal p=0.4837[a])	
Rate of sustained haematological improvement	Rate of improvement in haemoglobin, %	[redacted]	[redacted]
	Rate ratio for improvement in haemoglobin (95% CI; p-value)	[redacted]	
	Rate of improvement in platelet count, %	[redacted]	[redacted]
	Rate ratio for improvement in platelet count (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in FACIT-Fatigue scored	Median, months (95% CI)	5.59 (3.81, 11.20)	3.75 (2.20, 5.75)
	HR (95% CI; p-value)	1.37 (95% CI: 0.959, 1.954; nominal p=0.0776[a])	
Additional Secondary Endpoints			
DOR among patients with IRC-assessed PR or better	Median, months (95% CI)	[redacted]	[redacted]
TTNT	Median, months (95% CI)	NE ([redacted]	NE [redacted]
	HR (95% CI; p-value)	0.15 (0.06, 0.35; [redacted]	

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
Time to first meaningful deterioration in FACIT-Fatigue scored	Median, months	8.15 (3.98, 10.94)	14.03 (8.61, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EQ-5D-5L VAS scored	Median, months (95% CI)	[redacted]	
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EQ-5D-5L VAS scored	Median, months	8.34 (5.65, NE)	24.18 (11.27, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EQ-5D-5L Utility scored	Median, months	[redacted]	
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EQ-5D-5L Utility scored	Median, months	14.29 (8.15, NE)	24.11 (8.34, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EORTC-QLQ-30 Global Health Status scored	Median, months	[redacted]	
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EORTC QLQ-C30 Global Health Status scored	Median, months	14.95 (8.38, NE)	24.18 (13.86, NE)
	HR (95% CI; p-value)	[redacted]	
Reduction of TLS risk	Proportion with high risk of TLS at baseline reduced to medium/low,[e] n (%)	[redacted]	

BM = bone marrow; CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; del11q = 11q deletion; DOR = duration of response; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQoL-5 Dimension-5 Levels; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; O-Clb = obinutuzumab + chlorambucil; HR = hazard ratio; I+V = ibrutinib + venetoclax; IGHV = immunoglobulin heavy chain variable region; INV = investigator; IRC = Independent Review Committee; MRD = minimal residual disease; NE = not estimable; NGS = next generation sequencing; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient reported outcome; TLS = tumour lysis syndrome; TTNT = time to next treatment; VAS = visual analogue scale

[a] p-value is from a log-rank test stratified by IGHV mutational status and presence of del11q

[b] Results are presented based on the primary analysis; no additional assessment of MRD status by NGS was performed after the primary analysis

[c] p-value is from a Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status and presence of del11q

[d] Results are presented based on the primary analysis; no additional assessment of PRO measures was performed after the primary analysis

[e] After three cycles of ibrutinib monotherapy

[f] Results are presented based on the primary analysis; no analysis on reduction of TLS risk was conducted during extended follow-up

Source: Janssen Research & Development LLC [Data on File], 2021;[21] Kater, 2022;[26] Clinicaltrials.gov, 2022;[27] Janssen Research & Development LLC [Data on File], 2021[30]

Table 11 Summary of clinical effectiveness at a median follow-up of 27.7 months (GLOW; ITT primary analysis) [reproduced from Table 101, Appendix M of the CS]

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
Primary Endpoint			
IRC-assessed PFS	Median, months (95% CI)	NE (31.2, NE)	21.0 (16.6, 24.7)
	Rate at 24 months, % (95% CI)	84.4 (75.8, 90.1)	44.1 (34.2, 53.6)
	HR (95% CI; p-value)	0.22 (0.13, 0.36; nominal p<0.0001[a])	
INV-assessed PFS (supplementary analysis)	Median, months (95% CI)	NE (NE, NE)	[redacted]
	Rate at 24 months, % (95% CI)	[redacted]	[redacted]
	HR (95% CI; p-value)	HR 0.21; 95% CI: 0.12, 0.36; nominal p<0.0001[a])	
Key Secondary Endpoints Tested in a Hierarchical Manner			
MRD negative rate in bone marrow by NGS	Rate, % (95% CI)	55.7 (46.2, 65.1)	21.0 (13.2, 28.7)
	Rate ratio (95% CI; p-value)	2.65 (1.75, 3.99; p<0.0001[b])	
IRC-assessed CR (CR/CRi) rate	Rate, % (95% CI)	38.7 (29.4, 48.0)	11.4 (5.3, 17.5)
	Rate ratio (95% CI; p-value)	3.43 (1.91, 6.15; p<0.0001[b])	
IRC-assessed ORR	Rate, % (95% CI)	86.8 (80.3, 93.2)	84.8 (77.9, 91.6)
	Rate ratio (95% CI, p-value)	1.02 (0.92, 1.14; p=0.6991[b])	
OS	Median, months (95% CI)	NE (NE, NE)	32.5 (32.5, NE)
	Rate at 24 months, % (95% CI)	90.4 (82.9, 94.7)	91.3 (83.9, 95.4)
	HR (95% CI, p-value)	1.05 (0.45, 2.42; nominal p=0.9121[a])	
Rate of sustained haematological improvement	Rate of improvement in haemoglobin, %	44.3	50.5
	Rate ratio for improvement in haemoglobin (95% CI; p-value)	[redacted]	
	Rate of improvement in platelet count, %	24.5	29.5

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
	Rate ratio for improvement in platelet count (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in FACIT-Fatigue score	Time, months	5.59 (3.81, 11.20)	3.75 (2.20, 5.75)
	HR (95% CI; p-value)	[redacted]	
Additional Secondary Endpoints			
DOR among patients with IRC-assessed PR or better	Median, months (95% CI)	28.9 (28.68, NE)	21.1 (15.93, 25.10)
TTNT	Median, months (95% CI)	NE (NE, NE)	NE (31.5, NE)
	HR (95% CI; p-value)	0.14 (0.05, 0.41; nominal p<0.0001[a])	
Reduction of TLS risk	Proportion with high risk of TLS at baseline reduced to medium/low,[c] n (%)	84.6	Not applicable
Time to first meaningful deterioration in FACIT-Fatigue score	Median, months	8.15 (3.98, 10.94)	14.03 (8.61, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EQ-5D-5L VAS score	Median, months (95% CI)	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EQ-5D-5L VAS score	Median, months	8.34 (5.65, NE)	24.18 (11.27, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EQ-5D-5L Utility score	Median, months	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful deterioration in EQ-5D-5L Utility score	Median, months	14.29 (8.15, NE)	24.11 (8.34, NE)
	HR (95% CI; p-value)	[redacted]	
Time to first meaningful improvement in EORTC-QLQ-C30 Global Health Status score	Median, months	[redacted]	[redacted]
	HR (95% CI; p-value)	[redacted]	
	HR (95% CI; p-value)	[redacted]	
	Median, months	14.95 (8.38, NE)	24.18 (13.86, NE)

Endpoint	Outcome	I+V (n=106)	O-Clb (n=105)
Time to first meaningful deterioration in EORTC QLQ-C30 Global Health Status score	HR (95% CI; p-value)	[redacted]	

CI = confidence interval; CR = complete response; CRi = complete response with incomplete bone marrow recovery; del11q = 11q deletion; DOR = duration of response; EORTC-QLQ-C30; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQoL-5 Dimension-5 Levels; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; O-Clb = obinutuzumab + chlorambucil; HR = hazard ratio; I+V = ibrutinib + venetoclax; IGHV = immunoglobulin heavy chain variable region; IRC = Independent Review Committee; INV = investigator; MRD = minimal residual disease; NE = not estimable; NGS = next generation sequencing; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; TLS = tumour lysis syndrome; TTNT = time to next treatment; VAS = visual analogue scale

[a] p-value is from a log-rank test stratified by IGHV mutational status and presence of del11q

[b] p-value is from a Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status and presence of del11q

[c] After three cycles of ibrutinib monotherapy

Source: Janssen Research & Development LLC [Data on File], 2021;[21] Kater, 2022;[26] Janssen Research & Development LLC [Data on File], 2021[30]

3.2.3 Subgroup analyses

Details of subgroup analyses are presented in Document B, section B.2.7 and Appendix E of the CS.

CAPTIVATE FD: High-risk disease subgroup

At primary analysis, the CR/CRi rate of participants with del17p/TP53 mutation (i.e. high-risk disease; n=27) was 55.6% (95%CI 36.8, 74.3) as compared to 55.0% (95%CI 46.5, 63.6%) in those without del17p/TP53 mutation. The CR/CRi rate was maintained by the high-risk group until the time of extended analysis [redacted] At 36 months, the Kaplan-Meier point estimates for investigator-assessed PFS in high-risk patients were 80% [redacted] versus 88% [redacted] for all patients and 96% [redacted] versus 98% [redacted] respectively, for OS.

CAPTIVATE FD: CR/CRi [other subgroups]

At the time of the primary analysis (median follow-up 27.9 months), investigator assessed CR/CRi was consistent across the majority of specified sub-groups, with the exceptions of the bulky disease<5cm (66%) as compared to the ≥5cm subgroups (31%) and the mutated IGHV subgroup (47%) versus the unmutated IGHV subgroup (62%). Investigator-assessed CR rate for all subgroups did not change substantially after extended follow-up.

GLOW: PFS

At the time of primary analysis, improvements in IRC-assessed PFS were consistent across all subgroups, with the exceptions of race (white versus non-white) and diagnosis (CLL versus SLL). Hazard ratios for patients categorized as high-risk were not substantially different from those categorized as not high-risk.

The EAG does not have major concerns about the subgroup analyses reported in the CS.

3.2.4 Adverse events

Treatment-emergent adverse events (TEAEs)

In both CAPTIVATE FD and GLOW, the safety populations consisted of all participants who received at least one dose of study drug. Overviews of treatment-emergent adverse events (TEAEs) are reported in Document B, Tables 18 and 19 of the CS for CAPTIVATE FD (median follow-up 27.9 months) and GLOW (median follow-up 27.7 months), respectively, and presented as Table 12 below. The median treatment duration was 13.8 months for both CAPTIVATE FD and the I+V arm of GLOW and 5.1 months for the O-Clb arm of GLOW.

Table 12 Summary of TEAEs in CAPTIVATE FD and GLOW (safety populations, primary analysis) [adapted from Tables 18 and 19, Document B of the CS]

TEAEs, n (%)	CAPTIVATE FD	GLOW	
	I+V (n=159)	I+V (n=106)	O-Clb (n=105)
Any TEAE	158 (99.4)	105 (99.1)	99 (94.3)
Any Grade ≥3 TEAE	99 (62.3)	80 (75.5)	73 (69.5)
Any serious TEAE	36 (22.6)	49 (46.2)	29 (27.6)
TEAEs leading to discontinuation[a]	8 (5.0)	22 (20.8)	8 (7.6)
TEAEs leading to dose reduction[a]	33 (20.8)	28 (26.4)	22 (21.0)
TEAEs leading to dose interruption[a]	NR	[redacted]	[redacted]
Death	1 (0.6)	7 (6.6)	2 (1.9)

Median follow-up: CAPTIVATE FD, 27.9 months; GLOW, median 27.7 months
I+V, ibrutinib+venetoclax; O-Clb, Obinutuzumab+chlorambucil; TEAE, treatment-emergent adverse event; [a]of any study drug

Almost all participants in both studies experienced a TEAE with around two-thirds to three-quarters experiencing Grade ≥3 TEAEs. Serious TEAEs occurred in around one-quarter of participants of CAPTIVATE FD and the O-Clb arm of GLOW but nearly half of the I+V arm in the latter study. The company reported that incidence of serious TEAEs in GLOW during the first 6 months of treatment (to mirror the treatment duration of O-Clb) was similar across the I+V and O-Clb groups (34.0% and 26.7%, respectively). The EAG notes that the incidence of serious TEAEs in CAPTIVATE FD (22.6%) was around half of that in the I+V arm of GLOW (46.2%), with these two groups having the same treatment duration. Treatment-emergent AEs

leading to discontinuation of any study drug were higher in the I+V arm of GLOW (20.8%) than the O-Clb arm (7.6%) or the CAPTIVATE FD cohort (5.0%). The company reported that discontinuation rates in GLOW were similar across the I+V and O-Clb arms during the first 6 months of study treatment (11.3% and 7.6%, respectively). There was one death in CAPTIVATE FD, during the ibrutinib lead-in period, which was assessed by the investigator as possibly related to ibrutinib. In GLOW, a total of nine participants (7/106 in the I+V group, 2/105 in the O-Clb group) died due to TEAEs. Four of the seven deaths in the I+V arm occurred during ibrutinib lead-in treatment (the fatal TEAEs being pneumonia, malignant neoplasm and cardiac arrest). The remaining three deaths were during combination I+V treatment, with the fatal TEAEs being ischaemic stroke (n=1) and sudden death (n=2). In each group, one death was assessed by the investigator as related to the study treatment.

Table 13 presents a summary of TEAEs reported by CAPTIVATE FD (median 27.9 months follow-up) and GLOW trials (median 27.7 months follow-up). The most reported TEAE in participants treated with I+V was diarrhoea (62.3% in CAPTIVATE FD, 50.9% in GLOW I+V arm), with 3.1% and 10.4% of these, respectively, being Grade ≥3 TEAEs. Other commonly reported TEAEs in the I+V groups were nausea (42.8% and 26.4%, respectively), neutropenia (41.5% and 41.5%, respectively), arthralgia (33.3% and 11.3%, respectively), fatigue (24.5% and 15.1%, respectively) and vomiting (22.0% and 14.2%, respectively). The most reported Grade ≥3 TEAE in the I+V-treated participants in CAPTIVATE FD and GLOW was neutropenia (32.7% and 34.9%, respectively). In the O-Clb arm of GLOW, the most reported TEAEs of any grade were neutropenia (58.1%), infusion-related reaction (29.5%), thrombocytopenia (26.7%) and nausea (25.7%). The most reported TEAEs of grade≥3 were neutropenia (49.5%) and thrombocytopenia (20.0%).

In CAPTIVATE FD, TEAEs assessed by the investigator as being related to ibrutinib treatment were reported in 92.5% of patients, and those related to venetoclax in 84.3% of patients. In GLOW, these proportions were [redacted] in the I+V group and [redacted] in the O-Clb group.

Serious TEAEs

Serious TEAEs were reported in 22.6% of participants in CAPTIVATE FD, the most common being cellulitis (2.5%), pneumonia (1.9%) and atrial fibrillation, dyspnoea, hyponatraemia and vomiting (1.3% each). In the I+V arm of GLOW, the most reported serious TEAEs were atrial fibrillation (6.6%) and pneumonia (5.7%) and, in the O=Clb arm, pneumonia (5.7%) and febrile neutropenia (2.9%).

Table 13 Summary of TEAEs by system organ class and preferred term reported in CAPTIVATE FD (median follow-up 27.9 months) and GLOW (median follow-up 27.7 months) (incidence in any group ≥20% for any grade events or ≥2% for grade ≥3 events) [adapted from Tables 44 and 46, Appendix F of the CS, Table 14.3.1.3.1 of the CAPTIVATE CSR and Tables 18 and 21 of the GLOW CSR]

TEAEs by preferred term, n (%)	CAPTIVATE FD (n=159)		GLOW I+V (n=106)		GLOW O-Clb (n=105)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Gastrointestinal disorders	[redacted]	[redacted]	71 (67.0)	14 (13.2)	43 (41.0)	4 (3.8)
Diarrhoea	99 (62.3)	5 (3.1)	54 (50.9)	11 (10.4)	13 (12.4)	1 (1.0)
Nausea	68 (42.8)	2 (1.3)	28 (26.4)	0 (0)	27 (25.7)	0 (0)
Vomiting	35 (22.0)	[redacted]	15 (14.2)	1 (0.9)	14 (13.3)	0 (0)
Infections and infestations	106 (66.7)	13 (8.2)	64 (60.4)	18 (17.0)	51 (48.6)	12 (11.4)
Upper respiratory tract infection	37 (23.3)	[redacted]	13 (12.3)	0 (0)	14 (13.3)	0 (0)
Pneumonia	[redacted]	[redacted]	11 (10.4)	7 (6.6)	10 (9.5)	6 (5.7)
Cellulitis	[redacted]	[redacted]	1 (0.9)	1 (0.9)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	52 (49.1)	10 (9.4)	27 (25.7)	1 (1.0)
Rash	[redacted]	[redacted]	18 (17.0)	4 (3.8)	7 (6.7)	0 (0)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	36 (34.0)	8 (7.5)	27 (25.7)	0 (0)
Arthralgia	[redacted]	[redacted]	12 (11.3)	1 (0.9)	7 (6.7)	0 (0)
Muscle spasms	47 (29.6)	[redacted]	9 (8.5)	0 (0)	2 (1.9)	0 (0)
Blood and lymphatic system disorders	[redacted]	[redacted]	56 (52.8)	36 (34.0)	72 (68.6)	58 (55.2)
Neutropenia	66 (41.5)	52 (32.7)	44 (41.5)	37 (34.9)	61 (58.1)	52 (49.5)
Increased tendency to bruise	35 (22.0)	[redacted]	NR	NR	NR	NR
Thrombocytopenia	21 (13.2)	[redacted]	12 (11.3)	6 (5.7)	28 (26.7)	21 (20.0)
Anaemia	[redacted]	[redacted]	19 (17.9)	3 (2.8)	19 (19.1)	2 (1.9)

TEAEs by preferred term, n (%)	CAPTIVATE FD (n=159)		GLOW I+V (n=106)		GLOW O-Clb (n=105)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
General disorders and administration site conditions	[redacted]	[redacted]	42 (39.6)	7 (6.6)	44 (41.9)	3 (2.9)
Fatigue	39 (24.5)	1 (0.6)	16 (15.1)	1 (0.9)	10 (9.5)	0 (0)
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	38 (35.8)	3 (2.8)	30 (28.6)	2 (1.9)
Nervous system disorders	[redacted]	[redacted]	32 (30.2)	5 (4.7)	21 (20.0)	2 (1.9)
Headache	40 (25.2)	[redacted]	7 (6.6)	0 (0)	5 (4.8)	1 (1.0)
Injury, poisoning and procedural complications	[redacted]	[redacted]	25 (23.6)	6 (5.7)	36 (34.3)	6 (5.7)
Infusion-related reaction	NR	NR	0 (0)	0 (0)	31 (29.5)	3 (2.9)
Metabolism and nutrition disorders	[redacted]	[redacted]	45 (42.5)	16 (15.1)	25 (23.8)	11 (10.5)
Tumour lysis syndrome	0 (0)	0 (0)	0 (0)	0 (0)	6 (5.7)	6 (5.7)
Hyponatraemia	[redacted]	[redacted]	6 (5.7)	6 (5.7)	1 (1.0)	0 (0)
Hyperuricaemia	[redacted]	[redacted]	NR	4 (3.8)	NR	2 (1.9)
Investigations	[redacted]	[redacted]	36 (34.0)	18 (17.0)	27 (25.7)	12 (11.4)
Neutrophil count decreased	[redacted]	[redacted]	11 (10.4)	9 (8.5)	9 (8.6)	7 (6.7)
Vascular disorders	[redacted]	[redacted]	27 (25.5)	9 (8.5)	24 (22.9)	2 (1.9)
Hypertension	25 (15.7)	9 (5.7)	14 (13.2)	8 (7.5)	5 (4.8)	2 (1.9)
Cardiac disorders	[redacted]	[redacted]	26 (24.5)	15 (14.2)	14 (13.3)	3 (2.9)
Atrial fibrillation	[redacted]	[redacted]	15 (14.2)	7 (6.6)	2 (1.9)	0 (0)
Cardiac failure	[redacted]	[redacted]	NR	4 (3.8)	NR	0 (0)

NR, not reported

Adverse events of clinical interest

A summary of TEAEs of clinical interest from the safety populations of CAPTIVATE FD (median follow-up 27.9 months) and GLOW (median follow-up 27.7 months) is presented as Table 14 below.

Table 14 Summary of TEAEs of clinical interest (CAPTIVATE FD and GLOW, safety populations, primary analyses) [adapted from Tables 45 and 47, Appendix F of the CS; Table 14.3.1.2.1 of the CAPTIVATE CSR; and Section 7.2.5.4 of the GLOW CSR]

	CAPTIVATE FD I+V (n=159)	GLOW I+V (n=106)	GLOW O-Clb (n=105)
TEAEs of clinical interest			
Treatment-emergent major haemorrhage events	3 (1.9)	[redacted]	[redacted]
Grade ≥3 treatment-emergent major haemorrhagic event	[redacted]	[redacted]	[redacted]
Select any grade TEAE relevant to ibrutinib therapy			
TLS	0 (0)	0 (0)	6 (5.7)
Leukostasis	[redacted]	[redacted]	[redacted]
Neutropenia	66 (41.5)	36 (34.0)	56 (53.3)
Thrombocytopenia	21 (13.2)	12 (11.3)	28 (26.7)
Neutrophil count decreased	16 (10.1)	11 (10.4)	9 (8.6)
Anaemia	11 (6.9)	19 (7.9)	19 (18.1)
Platelet count decreased	7 (4.4)	3 (2.8)	1 (1.0)
Febrile neutropenia	1 (0.6)	2 (1.9)	3 (2.9)
Infections and infestations	106 (66.7)	64 (60.4)	51 (48.6)
Sepsis	[redacted]	1 (0.9)[b]	0 (0)[b]
Atrial fibrillation	7 (4.4)	15 (14.2)	2 (1.9)
Cardiac arrhythmia excluding atrial fibrillation	[redacted]	15 (14.2)	11 (10.5)
Cardiac failure	1 (0.6)	5 (4.7)	1 (1.0)
Other malignancy	[redacted]	8 (7.5)	10 (9.5)
Hypertension	2 (16)	15 (14.2)	5 (4.8)
Hepatobiliary disorders	[redacted]	NR	NR
Interstitial lung disease	[redacted]	[redacted]	[redacted]
Ischaemic stroke	0 (0)	3 (2.8)	0 (0)
Diarrhoea	99 (62.3)	54 (50.9)	13 (12.4)
Embryofoetal toxicity	0 (0)	0 (0)	0 (0)
Cytopenia	NR	59 (55.7)	74 (70.5)
Hepatic toxicity including hepatic failure	[redacted]	7 (6.6)	4 (3.8)

Median follow up: CAPTIVATE, 27.9 months; GLOW, 27.7 months
[a]Table 14.3.1.2.1 of CSR: Hepatotoxicity; [b]Table TSFAE26 of CSR: Septic shock

The focus of the section on AEs of clinical interest in the CS is on haemorrhagic events and TEAEs relevant to ibrutinib therapy.

There were few treatment-emergent major haemorrhage events in CAPTIVATE FD (1.9%) and the GLOW O-Clb arm (7.6%) as compared to around one-third of participants in the I+V arm of GLOW (34.9%);

[redacted]. Other commonly reported TEAEs of any grade relevant to ibrutinib treatment were infections and infestations (66.7% in CAPTIVATE FD, 60.4% in GLOW I+V arm, 48.6% in GLOW O-Clb arm), neutropenia (41.5%, 34.0%, 53.3%, respectively) and diarrhoea (62.3%, 50.9%, 12.4%, respectively). Rates of cytopenia were higher in the O-Clb arm of GLOW (70.5%) than the I+V arm (55.7%) but was not reported in the CAPTIVATE FD cohort.

Extended follow-up

The CS states that

[redacted]

Overall, the EAG's clinical expert is of the opinion that the adverse events reported in the CS are what is expected from clinical use of the relevant drugs and other studies and has no concerns.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company identified E1912, CLL14 and, ELEVATE-TN trials along with CPATIVATE FD cohort and GLOW trials for inclusion in the indirect treatment comparisons for the FCR suitable and unsuitable populations. Details of these trials

are in Appendix D of the CS. Relevant points for each trial are examine in the critique of the ITC in the following section.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

FCR-suitable population

The company employed indirect treatment comparison methods to estimate the efficacy of I+V versus FCR given that the CAPTIVATE FD cohort was a single arm trial. The E1912 trial that studied FCR and ibrutinib + rituximab (I+R) treatment efficacy in adults with previously untreated CLL who were eligible for FCR was chosen as the preferred comparator trial because of access to individual patient data and the comparability of the patients enrolled into both trials. However, the E1912 trial excluded patients with del17p while these patients were allowed in the CAPTIVATE study FD cohort, so only the 136 of the 159 patients without del17p were included in the ITC. The company employed inverse probability for treatment weighting (IPTW) with ATT weighting as the primary approach (average treatment effect in the control population (ATC; i.e., adjusting to the FCR arm of E1912) and average treatment effect in the combined/overall population (ATO) were used as scenario analyses to explore robustness of the results).

The results of this analysis are reproduced in Table 15 (Table 17 of Document B of the company submission and Table 20 of the appendices).

Table 15 I+V vs. FCR PFS results summary [Adapted from Table 17, Document B, and Table 20, Appendix D, of the CS]

	Unadjusted HR (95% CI) p-value	ATT HR (95% CI) p-value	ATC HR (95% CI) p-value	ATO HR (95% CI) p-value
All treated patients without del17p excluding any with missi	[redacted]	[redacted]	[redacted]	[redacted]

	Unadjusted HR (95% CI) p-value	ATT HR (95% CI) p-value	ATC HR (95% CI) p-value	ATO HR (95% CI) p-value
ng covariate values				
All treated patients without del17p including any with missing covariate values	[redacted]	[redacted]	[redacted]	[redacted]

* ATC is used in the economic modelling, see **Error! Reference source not found.**
TC = average treatment effect in the control population; ATO = average treatment effect in the overall population; ATT = average treatment effect in the treated population; CI = confidence interval; del17p = 17p deletion; HR = hazard ratio

I+V did not demonstrate statistically significant PFS advantage over FCR for all treated patients without del17p using the primary (ATT) approach

[redacted]

when excluding and including patients with missing covariate data, respectively, but did in the scenario analyses (ATC and ATO) although the HRs were broadly aligned and in the same direction.

The company note that the ATC analysis in which the CAPTIVATE FD cohort is matched to E1912 FCR group for all treated patients was considered as the base case in the economic modelling, given that the FCR arm of the E1912 trial was used as the reference curve in the model.

FCR-unsuitable population

I+V vs. VenO

The company identified the CLL14 trial along with the GLOW trial to carry out an anchored matching-adjusted indirect comparison (MAIC). The CLL14 study compared VenO vs. O-Clb for efficacy and safety with PFS by INV assessment as the primary endpoint. As both trials had O-Clb as comparators, the company considered anchored forms of ITC (Bucher and MAIC). The company argued that due to notable differences in the inclusion/exclusion criteria, as well as in patient baseline characteristics which were considered to be treatment-effect modifiers, anchored MAIC analyses were preferred over Bucher analyses. The first step was the analysis exclusion of patients from the GLOW population who would not have been eligible for the CLL14 study based on the inclusion criteria differences identified (those without either CIRS score >6 or CrCl>70 mL/min). In order to have an acceptable trade-off between matching characteristics and retained effective sample size in the base case matched population, only the following characteristics identified as the most important factors (based on feedback from a clinical advisory board held in the UK in September 2021 and the cut-off for the UK was selected based on feedback from an advisory board of clinical and health economic experts from the UK conducted in March 2022) were matched in the comparison of I+V and VenO:

- Age
- ECOG PS
- CIRS score
- TP53mut status

A fully matched (9 characteristics) analysis was carried out as a sensitivity analysis.

The EAG is in broad agreement with this approach as a fully matched analysis reduced the effective sample size to 48 with the attendant greater uncertainty.

The results of the MAIC are shown in Figure 8 (reproduced from Figure 17 of Document B of the company submission).

The unadjusted HR for PFS did not significantly favour I+V ([redacted]). A similar result was obtained after adjusting for the four top-ranked characteristics [redacted] The HR for PFS

after full adjustment (9 characteristics) was [redacted] which significantly favours I+V.

The EAG notes that although the HRs did not reach significance at any of the steps, the direction of the point estimates favour I+V.

The company noted that there was evidence suggesting that the proportional hazards (PH) assumption was violated in GLOW and CLL14 for PFS and conducted scenario analyses by applying time-varying HR to investigate the impact on the results. In this analysis, matching the four top-characteristics, for time period >12 months, the HR was [redacted], indicating a trend for advantage of I+V over VenO.

The EAG notes that issues with the assumption of proportional hazards add another level of uncertainty to results from a Cox regression. The company tried to mitigate this by carrying out a time-varying HR analysis, but the results were such that the degree of uncertainty around the HR (as indicated by the wide confidence interval) render such results unreliable.

Figure 8 PFS INV anchored MAIC results comparing I+V (month follow-up) and VenO (month follow-up) [reproduced from Figure 17, Document B of the CS]

CI = confidence interval; CLL = chronic lymphocytic leukaemia; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TP53 = tumour protein 53

I+V versus acalabrutinib

The ELEVATE-TN study was identified as the basis of regulatory approval for acalabrutinib in previously untreated CLL in the EU, with no other phase III studies being cited in the SmPC in support of this indication. The ELEVATE-TN trial was a three-arm study that compared acalabrutinib monotherapy vs. O-Clb and acalabrutinib + obinutuzumab vs. O-Clb for efficacy and safety. PFS by IRC assessment was the primary endpoint. As with the VenO comparison, anchored forms of ITC (Bucher and anchored MAIC) were considered since both ELEVATE-TN and Glow trials had O-Clb as comparators. Similar to the VenO comparison above, there were notable differences in the inclusion/exclusion criteria, as well as in patient baseline characteristics which were considered to be treatment-effect modifiers. anchored MAIC analyses were therefore preferred over Bucher analyses.

No exclusion of patients from the GLOW population who would not have been eligible for the ELEVATE-TN trial because no such criteria were identified. Four characteristics (Age, ECOG PS, CIRS score, TP53 mutation status) were matched in the comparison of I+V vs. acalabrutinib.

The results of the analyses for PFS (based on matching to the four characteristics listed above) are presented in Figure 9 (reproduced from Figure 18 of Document B of the company submission). Without adjusting for baseline patient characteristics between the GLOW and ELEVATE-TN studies, the HR for PFS was [redacted]). After applying the ELEVATE-TN exclusion criteria and matching of four characteristics, the HR for PFS was [redacted]). In the sensitivity analysis matching 16 characteristics available (fully matched population), the HR for PFS ([redacted]) indicated similar outcomes between I+V and acalabrutinib.

Due to the violation of the proportional hazard assumption, a time-varying MAIC was explored. For the time period >12 months, the HR was [redacted] after applying the ELEVATE-TN exclusion criteria and matching of four characteristics, indicating a trend towards a better outcome with I+V than with acalabrutinib. *However, the confidence intervals indicate a great degree of uncertainty around this estimate of effect and the results may not be reliable*.

The EAG notes that the results for the base case and the sensitivity analyses do not significantly favour I+V and the point estimates are close to unity.

The EAG would like also to draw attention to the fact that in many clinical trials there is a significant difference in outcome for patients with IGHV unmutated versus IGHV mutated CLL. Patients with IGHV unmutated disease have a significantly shorter progression free survival when treated with chemoimmunotherapy and some patients with IGHV mutated disease have very long progression free survival of over 10 years when treated with FCR. Given that there is enhanced BCR pathways signalling in the IGHV unmutated group there is a biological rationale for the use of BTK inhibitors in this group. Furthermore, data from previous studies using BTK inhibitors show that the IGHV unmutated group demonstrate efficacy in this group equivalent to the IGHV mutated group (e.g., RESONATE recent publication: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6899718/). The EAG Clinical expert suggests that an analysis of patients with IGHV unmutated CLL treated with ibrutinib and venetoclax, as compared to other treatments, may show a considerable benefit in this specific subgroup, which typically makes up 60-70% of patients in clinical trials. Whilst appreciating the difficulties in making any such analysis through indirect comparison, the EAG suggests this should be considered if possible.

Figure 9 PFS INV anchored MAIC results comparing I+V ([redacted] month follow-up) and acalabrutinib ([redacted] month follow-up) [reproduced from Figure 18, Document B of the CS]

CI = confidence interval; CIRS-G = Cumulative Illness Rating Scale-Geriatric; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TP53 = tumour protein 53

3.5 Additional work on clinical effectiveness undertaken by the EAG

No additional work has been carried out.

3.6 Conclusions of the clinical effectiveness section

The company submission identified two key trials to demonstrate clinical effectiveness of I+V. The FD cohort of CAPTIVATE, a single arm trial with an extended follow-up of 38.7 months informed the ITC. The EAG notes that none of the endpoints assessed attained follow-up times for 50% survival and median survival could not be computed and/or were considered unreliable. The I+V arm of GLOW with an extended follow-up of 34.1 months informed the MAICs. The GLOW trial compared I+V to O-Clb and demonstrated significant advantage of I+V over O-Clb in PFS, CR rate, TTNT, and MRD negative rate but not for ORR or OS in the extended follow-up (median 34.1 months) analysis. There was no significant difference between I+V and O-Clb in [redacted] *quality of life scores in the primary analysis (median 27.7 months) despite the longer duration of I+V treatment. The EAG also notes that the median survival time was not reached for most of the outcomes (especially for the I+V arm of the trial) due to the immature nature of the data. This has the consequence of increasing uncertainty around comparisons made using such data.*

The indirect treatment comparison approaches used in the CS is viewed as reasonable by the EAG. However, issues around the extrapolation of immature data and violation of proportionality assumption of the survival analyses further increase the uncertainty around the estimates presented especially those that have been used in implementing the economic models.

The EAG notes that, broadly, the ITC results do not present compelling evidence of any significant advantage of I+V over the comparators (FCR, VenO, acalabrutinib) for any of the outcomes examined in their base cases. There was evidence of I+V advantage over FCR only in the sensitivity analyses conducted.

While there is paucity of evidence of significant I+V superiority over the comparators, these results cannot then be interpreted as an indication of non-inferiority or equivalence because the key studies were not designed to investigate non-inferiority or equivalence.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company summarise their review of published cost-effectiveness studies in section B.3.1 of their submission document. They provide full details in Appendix G of their submission. Separate reviews of health-related quality of life and health care resource use studies were also undertaken by the company and are presented in Appendix H and I of their submission respectively. The focus of the review was on economic models used to assess the cost-effectiveness of first line therapy for CLL. The PICOS criteria are provided in appendix G of the CS (Table 48).

With respect to cost-effectiveness studies, the company identified 38, of which 19 took a UK health service perspective, with 15 of these evaluating a treatment of interest; nine UK HTA submissions and six published journal articles. Details of these 15 studies were tabulated for comparison in Table 57 of the CS (appendix G). The company identified that a Markov model was the most commonly used modelling approach, with monthly cycle length and 20–30-year time horizon commonly used. Three state partitioned survival models were also commonly used in HTA submissions to UK HTA agencies.

The EAG has no issues with the company's systematic review of cost-effectiveness evidence. They have been thorough in their approach to searching, data abstraction and quality appraisal. Based partly on their findings, the company have favoured the development of a de Novo semi-Markov model to address the decision problem in the current appraisal (section 4.2). In doing so, they have made close reference to the modelling assumptions used in the recent NICE appraisals of VenO and acalabrutinib for patients with untreated CLL.[9, 12] Further reference is made to TA429 (Ibrutinib for previously treated CLL and untreated CLL with 17p deletion or TP53 mutation)[31] and TA343 (Obinutuzumab in combination with chlorambucil for untreated CLL)[32] and TA359 (Idelalisib for treating CLL)[33] and TA487 (updated to TA796 Venetoclax for treating chronic lymphocytic leukaemia)[34] with respect to justifying modelling assumptions and inputs.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

A summary of how the company's economic case compares with the NICE reference case is provided in Table 16.

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligned with the reference case. Focuses on health effects for patients
Perspective on costs	NHS and PSS	Aligned with the reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligned with the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligned with the reference case
Synthesis of evidence on health effects	Based on systematic review	Yes. Efficacy inputs based on trial evidence and indirect IPTW comparison and anchored MAICs using selected studies identified by systematic review. The EAG has some concerns with the approach used to estimate individual transition probabilities of progression for the Markov model
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Aligned with the reference case; the EAG has some concerns regarding the face validity of the utility values for progression free on first line treatment and progression free on second line treatment.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligned with the reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligned with the reference case

Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligned with the reference case
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	Aligned with the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligned with the reference case
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company describe their model, in section B.3.2.3 of their submission document, as a semi-Markov model with four health states: progression free in first line treatment (PF1L), progression free in second line treatment PF 2L), disease progression (PPS), and death. Thus, the model relies on estimates of transition probabilities from:

- PF 1L to progression, with a proportion (100% in the base case) of those progressing assumed to receive second line treatment in PF 2L, and the reminder (0% in the base case) progressing directly PPS.
- PF 1L to death (pre-progression mortality)
- PF 2L to PPS
- PF 2L to death
- PPS to death.

Within the PF 1L and PF 2L states, patients can either remain on treatment until progression or stop treatment depending on whether they are on a fixed dose or treat to progression regimen.

The model uses array formulas to account for time since progression in the PF 2L health state. This is for the purpose of allowing for a 14 cycle delay between the time of progression and treatment initiation, and accurately modelling time on second line treatment. The tracking of time in the PF 2L state does not, however, extend to allowing subsequent transitions to be dependent on time in state. Thus, transitions form PF2 to PPS and death

follow exponential distributions (constant probabilities) capped by age/sex matched general population mortality, as does the transition to death from PPS.

The EAG believes the company's model structure is broadly appropriate for capturing the nature of disease progression and the relationship between progression and mortality. However, the EAG has some concerns regarding the way transition probabilities for progression have been estimated. This is discussed further under 4.2.6 below.

4.2.3 Population

The company outline the three distinct sub-populations considered in their economic case in section B.3.2.1 of their submission document; FCR-suitable, FCR-unsuitable, and high-risk patients. The company allude to the fact that there is not a universally agreed definition of FCR-suitable and FCR-unsuitable (B1.3.3) but define these using thresholds for CIRS, CrCl, ECOG performance status, age and comorbidity status:

- "FCR-suitable patients: patients with no del17p mutation, with CIRS ≤6, CrCl ≥70 mL/min and ECOG PS <2
- FCR-unsuitable patients: patients with no del17p mutation, with CIRS >6 and/or CrCl <70 mL/min who are ≥65 years old or 18-64 years old with comorbidity
- High-risk patients: Patients with del17p/TP53 mutation"

The company highlight the fact that patients with TP53 mutation have not been removed from the CAPTIVATE and GLOW trial cohorts informing model inputs for the FCR-suitable and FCR-unsuitable populations, and therefore they refer to them as those without a del17p mutation rather than those without del17p or TP53 mutation. The reasons given for this include comparability with the external cohorts informing the indirect treatment comparisons and to preserve randomisation (in the case of GLOW).

The EAGs clinical expert advisor broadly agrees with the company's definitions of the subpopulations, and the respective comparators considered appropriate for them in the company's economic case. Ideally patients with a TP53 mutation would be excluded from cohorts informing the FCR-suitable and unsuitable populations, as they form part of the separate high-risk population, but the EAG acknowledges that it is not possible to remove

those with a TP53 or dp17p/TP53 from the external cohorts used in the indirect treatment comparisons, and so accept company's reasoning. With few patients included with a TP53 mutation (7/136 in CAPTIVATE (non-del17p cohort) and 7/106 and 2/105 in the I+V and O-Clb arms of Glow), it is unlikely to have resulted in any significant bias in the modelling.

4.2.4 Interventions and comparators

The intervention (I+V) and comparators considered relevant by the company for each of the model sub-populations are described in section B.3.2.2 of their submission document. VenO was excluded as a comparator for the FCR-suitable patients because it is only available on the CDF in England for this population. BR was excluded by the company for patients without del17p/TP53 mutation, on grounds that its rarely used in clinical practice and no longer recommended in BSH guidelines, leaving only FCR as the comparator for the FCR-suitable population and O-Clb, VenO, and acalabrutinib as comparators for FCR-unsuitable population. Idelalisib with rituximab was excluded as a comparator for patients with del17p/TP53 mutation on grounds it is rarely used now in clinical practice due to a high risk of infection and death, leaving acalabrutinib, VenO, and ibrutinib as comparators in this high risk population. Details of the dosing schedules for the intervention and comparators in the respective populations are provided in Tables 22, 23 and 24 of the company submission.

The EAG's clinical expert advisor agrees with the company's arguments for excluding BR and idelalisib+rituximab. He is also in agreement with included comparators for each population.

4.2.5 Perspective, time horizon and discounting

The modelling adopts a lifetime horizon on health and personal social care costs and health benefits to patients. This is capped at 30 years for the FCR-unsuitable and high-risk populations (age 71 at baseline), and 40 years for the younger FCR-suitable population (age 58 at baseline). Future costs and health benefits are discounted using a discount rate of 3.5% in line with the NICE reference case.

The EAG is satisfied the perspective, time horizon and approach to discounting are aligned with NICE reference case but has some concerns regarding the plausibility of aspects of the model extrapolations over the selected time horizons (see 4.2.6).

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness is determined separately for the FCR-suitable and FCR-unsuitable populations. Treatment effectiveness in the high risk del17p/TP53 mutation group is assumed equal to that in the FCR-unsuitable population. The general approach for all populations is to fit/generate a PFS curve for each first line treatment option, and then remove the estimated hazard of pre-progression mortality from the fitted hazards of progression or death. This provides separate extrapolated hazards for progression and death for informing the model transition probabilities from PF 1L to progression and PF 1L to dead. A similar approach is used for informing the transition probabilities from PF 2L to PPS and PF 2L to dead, based on PFS data from a previously treated cohort. Finally, PPS to death is estimated based on post-progression survival of a cohort of CLL patients previously treated with 1 to 2 prior lines of therapy.

FCR suitable

PF 1L to PF 2L and death

The company describe their approach in detail in section B.3.3.2 of their submission.

Briefly, the company chose a reference PFS curve for the FCR comparator, derived from parametric survival analysis of reconstructed individual patient data (IPD) from the long-term follow-up of the E1912 trial (an earlier data cut of which was used for the inverse probability treatment weighted (IPTW) comparison between FCR and I+V). They then apply the hazard ratio for I+V versus FCR, from the IPTW analysis to the PFS FCR reference curve. This was done to overcome the challenges of extrapolating directly from the immature I+V PFS data for the CAPTIVATE FD cohort. The company argued that the PFS data from CAPTIVATE could not be relied upon for direct extrapolation due to its immaturity [redacted].

The EAG understand the company's concern regarding the immaturity of PFS data from CAPTIVATE but note that their approach of applying a hazard ratio to the PFS curve for FCR does not solve this problem and has its own uncertainties (below). The EAG asked the company to further justify this at the clarification stage, given that similarly immature PFS data for the I+V arm of GLOW was relied upon for extrapolation in the FCR unsuitable population. The company response reiterated their rational for choosing a reference curve based on the FCR arm of the E1912 trial but did also provide results of a scenario where the

reference curve in the model was a parametric curve fitted directly to the PFS data of the CAPTIVATE FD cohort. For this scenario, an exponential distribution was chosen for the I+V reference curve. The hazard ratio for FCR versus I+V was then applied to this. The results can be seen in Figure 2 and Table 7 of the company's response to the clarification letter. Under this scenario PFS increased for both I+V and FCR, resulting in higher total life years and QALYs, but the ICER was minimally affected. The EAG would note, however, that the choice of exponential parametric curve, guided only by the observation that PFS in the younger/fitter FCR suitable population should be higher (no worse) than in the FCR unsuitable population, is not very well justified.

The PFS curve fitting for FCR from the E1912 trial, informing the company's base case, identified the Weibull distribution as the preferred option based on a combination of statistical and visual fit, and long-term plausibility of extrapolation based on clinical expert opinion (Figure 10).

Figure 10 Parametric models overlaying the observed INV PFS KM data for FCR from E1912 (Source: Figure 21, Document B of the CS)

FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; KM = Kaplan-Meier; PFS = progression-free survival

The EAG is satisfied that the company's selected reference curve provides a reasonable extrapolation for FCR. However, derivation of the PFS curve for I+V relies on a

proportional hazards assumption being applied over the full time horizon of the model (Figure 11). The EAG was not satisfied that this had been appropriately justified, and so asked the company at the clarification stage to a) provide justification for proportional hazards based on the indirect IPTW comparison and b) explore scenarios where the relative treatment effect of I+V versus FCR waned over time in the model. In response, the company provided the naïve and adjusted Kaplan Meier plots for the IPTW comparison, and Schoenfeld residual plots/tests (see company response to clarification question B5). These do not contradict the assumption that proportional hazards hold over the observed follow-up duration of the IPTW analysis, but this does not mean that it will hold over the duration of the model. To support the application of proportional hazards in the longer term, the company highlight longer term follow up data (median 5.8 years) for ibrutinib (treat to progression) versus fixed dose FCR, which shows no obvious loss of effect for ibrutinib over this time period. However, whether this can be generalised to fixed dose I+V remains uncertain. To address the potential for waning effects, the company consulted clinical experts who suggested it is very hard to predict. One expert seems to have suggested if it were to happen it would be most likely do so between 5 to 10 year post treatment. Therefore, the company provided a number of scenarios in which the hazard ratio for I+V versus FCR wanes from [redacted] to 1 over a defined period of time in the model: 1) from 5 years to 15 years post treatment; 2) from 5 years 10 years post-treatment; and 3) from 10 years to 20 years post treatment. The EAG believes that these scenarios appropriately address the uncertainty. The waning assumptions do increase the ICER substantially, but it does remain below £30,000 across the three scenarios (not accounting for confidential discounts on comparators).

In terms of the hazard ratio used to derive the I+V curve, the company use the estimate of [redacted] obtained when weighting the I+V data for the CAPTIVATE FD cohort to the covariate distribution of the FCR arm of E1912. This was justified on grounds that the FCR arm of E1912 is used as the reference PFS curve in the model.

The EAG follow the company's reasoning but note that the magnitude and statistical significance of the hazard ratio for I+V versus FCR is sensitive to the IPTW weighting approach (see Table 29 of the company submission). The company have, however, addressed this uncertainty in scenario analysis.

Figure 11 I+V PFS capped by GPM derived from the HR vs. FCR reference curve (ATC analyses) (Source: Figure 22, Document B of the CS)

del17p = 17p deletion; FD = fixed duration; GPM = general population mortality; I+V = ibrutinib + venetoclax; KM = Kaplan-Meier; PFS = progression-free survival
I+V applied to the Weibull distribution from FCR PFS extrapolation

To estimate separate transition probabilities from PF 1L to progression and death, the company remove estimates of pre-progression mortality risk from the cycle specific risks of progression or death based on the derived PFS curves. Pre-progression mortality was calculated as annualised risks based on the IPD from the CAPTIVAE FD cohort and the FCR arm of E1912 (36.6m data cut). This suggested a lower annualised risk of death with I+V, which was also lower than age matched general population mortality from cycle 1. The company acknowledged that this may be implausible and so applied the estimate of annualised risk obtained from the FCR arm of E1912 for both FCR and I+V. It was further capped using age matched general population mortality, as were the PFS curves for logical consistency.

PF 2L to PPS and death

To model the transitions from PF 2L, the company used individual patient PFS data from a subgroup of CLL patients with 1-2 prior lines of therapy who received ibrutinib treatment in the RESONATE trial. RESONATE was preferred to E1912 due to the availability of long-term and individual patient data to enable estimation of post progression transitions.[14]

A parametric reference curve for the PFS data from RESONATE (1-2 prior treatment lines subgroup) was established based on statistical and visual fit, and plausibility of extrapolations. However, the model is unable to condition the risk of progression or death based on time in the PF 2L state, and so requires the use of an exponential (constant hazard) distribution. Nevertheless, the company note that the exponential distribution did in fact have the lowest AIC/BIC and provided extrapolations in the middle of the range of projections (Figure 12).

The company note that following progression on I+V or FCR, patients are eligible to receive ibrutinib, acalabrutinib or VenR. These are assumed to have equal efficacy in the base case analysis. They further note that the assumption of clinical equivalence between ibrutinib and acalabrutinib in R/R CLL was accepted in TA689 based on the outcomes of an ITC, and equal efficacy across subsequent treatments was accepted in TA663 and TA 689.[9, 12] This further assumes that the subsequent risks of progression and death are equivalent irrespective of first line treatment received.

Similar to the calculation of individual transitions to progression and death for PF 1L, the RESONATE IPD[14] is used to estimate an annualised pre-progression mortality risk, capped by aged matched general population mortality, which is removed from the fitted risk of progression or death from the PF 2L state.

The EAG's clinical advisor was broadly in agreement with the chosen source of data for informing the PF 2L transitions in the context of the company's positioning. He also generally agreed with the chosen extrapolation of the PFS data and the assumptions of equal efficacy between second line treatments. He did, however, note the potential for different subsequent treatments to perform better/worse in subgroups with/without IVHG mutation. Accepting the lack of available evidence comparing different treatments for CLL the EAG accepts the company's approach.

Figure 12 PFS extrapolations of ibrutinib (1-2 prior lines) from RESONATE trial final (65m) data cut (Source: Figure 23, Document B of the CS)

PFS = progression-free survival

PPS to death

Finally, the risk of death from the post progression survival (PPS) state is modelled from a constant annual mortality rate derived from the post progression survival data of patients in the ibrutinib arm (1-2 prior lines of therapy) of the RESONATE trial.[14] This is also capped by age/sex matched general population mortality.

The company note that some patients may receive further treatment following progression on second line treatment. They state, however, that there are no available data on treatment efficacy beyond second line, and so only model the constant risk of mortality from the PPS state.

The EAG note that it is not clear from the submission whether the subgroup of patients (1-2 prior lines of treatment) in the RESONATE trial, who inform the annual mortality rate from the PPS state in the model, received treatment following progression on ibrutinib. It is clear, however, that the index treatment in RESONATE represented the third line of treatment for a subgroup of patients, so it may have been possible to model a third line more explicitly.[35] The EAG's clinical expert advised that in the current treatment landscape most of the FCR fit population would likely receive a third line of treatment conditional on surviving to this stage in the pathway. They further suggested that a proportion of the FCR-unfit population would also be treated at third line. In this respect, the company's model could potentially

underestimate post-progression survival, underestimate post progression utility and/or fail to account for relevant post-progression treatment costs. Without knowing what proportion of patients in the RESONATE (1-2 prior treatments) subgroup that had further treatment following progression on ibrutinib, it is difficult to judge. It would, however, perhaps be reasonable to apply third line treatment costs in the PPS state to reflect this proportion. This would bring the state costs in line with the efficacy data that is used. This is not the case in the company's model.

FCR Unsuitable

PF 1L to PF 2L and death

For the FCR unsuitable population, the company independently fitted parametric survival curves to the PFS data from I+V and O-Clb arms of the GLOW trial (see section B.3.3.3 of the company submission for details).

For the I+V arm, the company explored the standard parametric curves, and selected the exponential based on a combination of statistical and a visual fit and plausibility of extrapolations. The chosen exponential curve provided the most pessimistic extrapolation but still required capping at general population mortality for logical consistency; the extrapolated hazard of progression or death converges with that of the age/sex matched general population mortality from approximately [redacted] years in the company's base case model, when approximately [redacted] of the I+V cohort remain alive and progression free (Figure 13). Since the fitted exponential curve did not provide a good visual fit to the early PFS events observed in the KM data, the company used the KM data directly for the first 15 cycles of the model, followed by the exponential distribution capped by general population mortality.

Figure 13 Parametric models overlaying the observed INV-assessed PFS KM data for I+V (Source: Figure 25 of the company submission, document B)

GPM = general population mortality; I+V = ibrutinib + venetoclax; INV = investigator; KM = Kaplan-Meier; PFS = progression-free survival

To calculate separate transition probabilities for progression and death for I+V from the PF 1L state, the company used Kaplan Meier estimates of pre-progression mortality from the I+V arm of the GLOW trial for the first 15 model cycles, and then used an annualised probability of death ( ) derived from the O-Clb arm of GLOW. The O-Clb arm of glow was used for the annualised mortality rate because only one death was observed beyond 15 months in the I+V arm. Subtraction of the calculated cycle probabilities of pre-progression mortality from the extrapolated cycle probabilities of progression or death gives the extrapolated probability of progression to PF 2L in the model.

For the O-Clb comparator in the FCR unsuitable population, the company explored standard parametric models but found that the curves did not provide good visual fit to the various inflection points in the observed KM data. They, therefore, fitted more complex parametric survival models. Based on consideration of visual and statistical fit, and alignment of extrapolations with clinical expectations, the company chose a seven-knot spline model for their base case. At the clarification stage they provided a figure comparing the various spline models against the observed KM data (Figure 14).

The EAG is broadly satisfied with the company's approach to modelling PFS for O-Clb in the FCR-unsuitable population. The data are relatively mature, and most of the more complex

curves to do not produce radically different extrapolations. That said, it would have been useful to see some further scenario analysis around the choice of parametric function.

Figure 14 Spline models and observed O-Clb PFS (Source: Figure 11 of the company's response to the clarification letter)

For the other comparators included in the FCR-unsuitable population (VenO and acalabrutinib monotherapy), the company apply the hazard ratios derived from the anchored MAICs (described in section 2.9 of their submission) to the selected PFS curve for I+V. The same rate of pre-progression morality as for O-Clb is assumed.

The company's approach to estimating the transition probability from PF 1L to PF 2L, by subtracting the estimated pre-progression risk of mortality (capped by general population mortality) from the extrapolated risk of progression or death (based on fitted PFS curves also capped by general population mortality), has some pronounced implications in the older FCR unsuitable cohort. With higher background mortality in this older group, the extrapolated PFS curves and pre-progression mortality both converge to age sex/matched general population mortality at an earlier stage in the model when a substantial proportion of the cohort remain alive and progression free. The calculated risk of progression (to PF 2L) becomes zero from this point onwards, inferring that a proportion of patients are essentially cured. Table 17 below shows the time in years and the proportion alive and progression free for each comparator when extrapolated risks of progression or death and pre-progression mortality converge. This appears to be more an artefact of the approach rather than a well justified assumption. It is a less obvious problem in the younger FCR suitable population where the background mortality for the age-sex matched general population is lower, resulting in the extrapolated risks of progression or death remining higher than general population over the majority of the modelled time horizon. Thus, the risk of progression remains non-zero for longer.

Given this issue, the EAG asked the company to further justify their approach and the implicit assumption that a proportion of patients are essentially cured with more effective treatments (i.e., face zero further risk of progression and a mortality rate in line with age/sex matched general population from the time shown in Table 17). The EAG also asked the company to explore methods that retained an ongoing risk of progression indefinitely over the time horizon of the model.

The company came back stating that "During the acalabrutinib NICE submission (TA689), a clinical expert indicated that functional cure (defined as PFS becoming similar to general population mortality hazards, such that patients do not experience any additional risk of progression or death due to CLL) was possible." They also stated that "During an advisory board conducted in March 2022 by Janssen, which included clinical experts from the UK, a clinical expert treating CLL patients indicated that patients not experiencing progression in 10 years may essentially be cured" (Company response the Clarification letter, QB6).

The company further highlight long-term PFS and OS data observed with frontline ibrutinib treatment for CLL in the RESONATE-2 trial, which shows "high survival rates are achievable with more than half of patients alive and still progression-free and 78% of patients alive at 7 years".[19]

The EAG acknowledges the company's arguments and accept there is the possibility that targeted therapies my lead to a functional cure for some patients. However, this remains uncertain given the paucity of longer term data; it remains unclear whether it is plausible to expect the progression risk to reach zero for any comparators. Further, as indicated, a cure fraction is not an explicit assumption in the company's case, and appears to be more an artefact of the modelling approach; i.e. why would there be a lower chance of cure with targeted therapies in the FCR suitable population, as the company modelling implies?

In their response to the clarification letter, the company explored an approach that results in a lower proportion of patients remaining in the PF 1L state in the long term. They achieve this by applying an SMR of 1.19 (or 2) to the age/sex matched general population mortality, to which PFS and pre-progression mortality are capped. This does reduce the proportion surviving in the progression free state over time, but it doesn't address the request to consider methods that retain a probability of progression (to PF 2L) throughout the model time horizon. In fact, with PFS and pre-progression mortality capped at the SMR adjusted general population mortality, the risk of incident progression is zeroed from an earlier time point when a larger proportion of the population are progression free. The EAG is concerned the company's approach to approximating the transitions to progression from PF 1L may potentially bias the comparisons in favour of more effective treatments.

Table 17 Timepoints from which zero incident progression occurs, and the corresponding proportion alive and progression free at these timepoints

Comparator	Time at which risks of progression or death (PFS) and pre-progression mortality converge at general population mortality (years)	Proportion of the cohort remaining alive and progression at this time point
I+V	[redacted]	[redacted]
O-Clb	[redacted]	[redacted]
VenO	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]

Notes: I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + Obinutuzumab; *Extrapolated risk of progression or death always remains higher than extrapolated risk of pre-progression mortality.

A further issue regarding the comparisons of I+V with VenO and acalabrutinib, is that they rely on the hazard ratios for PFS derived from the anchored MAICs. These comparative effectiveness estimates are uncertain due to potential differences between studies informing the comparisons. Their application in the model relies on the further assumption that proportional hazards hold over the time horizon of the model. The company have explored the application of time varying hazard ratios (≤ 12 month; >12 months) derived from the MAICs in scenario analysis, but these still assume proportional hazards hold indefinitely beyond 12 months. The hazard ratios derived from the MAIC are relevant to the observed follow-up period of the included studies (medians of [redacted]). Their application in the longer term is uncertain. The company have not explored the potential impact of these effects waning over time in the FCR-unsuitable population.

A further observation is that the HRs from the MAICs are not statistically significant at a 5% type 1 error level. Directionally, the point estimate supports a PFS benefit for I+V over VenO, but the confidence interval is wide and includes unity. The point estimate of the HR for I+V versus acalabrutinib is close to one ([redacted]) with a wide confidence interval

([redacted]). In this context, a scenario that assumes equal efficacy may also be worth considering.

PF 2L to PPS and death

The company follow exactly the same approach as they do for FCR-suitable population to estimate the remaining transitions in the model; i.e. they rely on the ibrutinib arm (1-2 prior lines subgroup) of the RESONATE trial to model second line PFS and pre-progression mortality for all subsequent treatments in the FCR-unsuitable population.

It is worth noting that this infers the PFS outlook is substantially better in the second line for those who receive O-Clb at fist line in the FCR unsuitable population.

High risk population

For the high-risk population, defined as those with del17p/TP53 mutation, the company assume equivalent efficacy to FCR-unsuitable patients. This is due to paucity of data available to inform clinical parameters in this small subgroup. The company note that the high risk subgroup will have a similarly poor prognosis as that of the FCR-unsuitable population, and that this assumption was used and accepted in the appraisal of acalabrutinib for CLL (TA689).[9] Since ibrutinib monotherapy is a relevant comparator in the high-risk population, a further assumption was made that it has equal efficacy to acalabrutinib. The company note that this assumption was also accepted in TA689.

Whilst not ideal, based on its own clinical feedback and the precedent set in TA689, the EAG accepts the company's approach to modelling the high-risk population. The EAG note that in TA689 the generalisation of equal comparative efficacy of *ibrutinib and acalabrutinib, from an indirect comparison in the second line treatment setting, was accepted.[9] Thus, the results of a CMA between acalabrutinib and ibrutinib based on data in the R/R setting, was considered applicable to high risks patients in the first line setting. This is slightly different to what the company propose, of generalising the reference curve for I+V from the broader population of FCR-unsuitable patients in the first line setting (and the corresponding comparative treatment effects of VenO and acalabrutinib) to high-risk patients in the first line setting. The EAG is satisfied with the assumption regarding equal efficacy of acalabrutinib and ibrutinib.*

4.2.7 Health related quality of life

The impact of CLL on health-related quality of life (HRQoL) is captured in the model in three ways: the HRQoL impact of the PF, PF2L and PPS health states; disutilities associated with treatment-related adverse events (AEs) in first-line; and disutilities associated with IV treatment administration.

HRQoL data collected in clinical trials

Quality of life data were collected in the GLOW trial using the EQ-5D-5L questionnaire in FCR-unsuitable patients. Data were collected on day 1 of cycles 1, 3 and 5 and every 12 weeks after cycle 5 prior to disease progression. Data were also collected at the end of treatment (30 days after the last dose) and at the first two post-treatment, post-PD visits (every 24 weeks). No quality of life data were collected in the CAPTIVATE trial.

The EQ-5D-5L data collected in GLOW were mapped to EQ-5D-3L using the 'EEPRU dataset' in accordance with the NICE methods guidance.[36] Missing data and values where progression status was unknown were removed from the analysis with no imputation performed. Descriptive statistics indicate no statistically significant treatment effect. The company notes that post-progression data are limited with only 51 post-progression observations compared to 1,723 pre-progression.

Table 18 below outlines the utility values derived from GLOW compared with age-adjusted population utility values.

Table 18 Pre- and post-progression utility from GLOW vs. age-adjusted general population utility (adapted from Tables 46 and 47, Document B of the CS)

Health condition	Estimate	Lower 95% CI	Upper 95% CI	Source
PF 1L	[redacted]	[redacted]	[redacted]	GLOW
Progressed disease	[redacted]	[redacted]	[redacted]	GLOW
No history of health condition: 'cancer'; age band: 65 to ≤70 years	0.808	0.794	0.821	Ara and Brazier 2011[37]

General population UK (age = 71; male = 57.8%)	0.798	NA	NA	HSE 2014[36]

1L = first line; CI = confidence interval; HSE = Health Survey for England; NA = not applicable; PF = progression-free; UK = United Kingdom

QoL data used in model

The pre-progression utility value derived from the GLOW trial is higher than population norms, which the company argued was plausible as high pre-progression values have been seen in other first-line CLL trials for comparator treatments (VenO and acalabrutinib monotherapy). A potential reason given for the high utility value was that patients may experience a relief of symptoms, resulting in an increase in their quality of life compared to their experience prior to treatment. On this basis, the pre-progression utility value from GLOW was used in the model base case, with age-adjustment applied to account for the younger age of the FCR-suitable population (59 years in CAPTIVATE compared to 71 years in GLOW).

The PD utility value from the GLOW trial was higher than values used in other models in comparable patient groups, which may reflect the low number of post-progression observations. As a result, a utility value of 0.6 was selected for the PD health state based on a study by Holzner et al,[38] which has been used and accepted by NICE in previous TAs in CLL.[9, 12] This value was applied to both the PF 2L and post 2L progression health states.

To capture the quality of life impact of IV administration in the model, an additional utility decrement of 0.04 was applied additively for each treatment requiring IV administration. Where more than one component of a treatment regimen required IV administration, the utility decrement was applied separately for each component. This approach may result in some double-counting of the impact of IV administration on quality of life for regimens with multiple IV components but the impact in terms of any bias in the model is likely minimal. Table 19 summarises the utility values used in the different patient populations in the model. Note that utility values for the high-risk population were assumed to be the same as the FCR-unsuitable population due to the lack of suitable alternative utility data for this group.

Table 19 Summary of utility values for cost-effectiveness analysis (adapted from Tables 52 and 53, Document B of the CS)

	FCR-suitable		FCR-unsuitable/high-risk	
State	**Utility value: mean (SE)**	**95% CI**	**Utility value: mean (SE)**	**95% CI**
PF 1L	[redacted]	[redacted]	[redacted]	[redacted]
PF 2L	[redacted]	[redacted]	[redacted]	[redacted]
Post 2L progression	[redacted]	[redacted]	[redacted]	[redacted]
Utility decrement due to IV treatment	[redacted]	[redacted]	[redacted]	[redacted]

*Derived from the utility from GLOW trial subject to age adjustment to match the starting age of the FCR-suitable population; ǂ SE was assumed to be the same as utility derived from GLOW; ᵻ Utility in PF 2L and Post progression were derived from external data subject to age adjustment to match the starting age of the FCR-suitable population

1L = first line; 2L = second line; CI = confidence interval; IV = intravenous; PF = progression free; SE = standard error

The use of the GLOW trial as the key data source for utility values is appropriate as it captures quality of life data in a relevant patient group who would receive I+V in practice. Despite this, there are face validity concerns with the PF utility value derived from GLOW as it is higher than aged-adjusted population norms for England (HSE 2014).[36] The company acknowledge this but argue the use of the high PF utility value is considered reasonable for the following reasons: firstly, as noted above, it is consistent with values derived in other relevant trials (e.g. VenO, acalabrutinib) where EQ-5D scores were of a similar value and higher than population norms. The CS notes that this may reflect EQ-5D being insensitive to some aspects of quality of life burden associated with CLL (e.g. fatigue) but more sensitive to other factors (e.g. depression, pain) which may be more prevalent in the general population. Secondly, the improvement in quality of life may reflect better symptom control once patients begin first-line treatment and experience relief from their symptoms. The EAG notes the similar PF utility values estimated from quality of life data collected in other trials, but argue it is likely that this reflects the better performance status of patients enrolled in clinical trials who tend to have fewer co-morbidities compared with patients who would receive the

treatment in routine clinical practice. Clinical expert advice to the EAG confirmed the PF utility value used in the model lacks face validity and a more realistic approach would be to cap the utility values at general population norms. This scenario analysis was provided at clarification stage where the PF utility for the FCR-suitable population was capped at 0.849 (age 58, 67.3% male) and for the FCR-unsuitable and high-risk populations it was capped at 0.798 (age 71, 57.8% male). The PF 2L and post-progression health state values remained unchanged at 0.6.

The results of this analysis are provided in Tables 11 – 13 in the clarification response and show some sensitivity to applying a more realistic PF utility value in the model, particularly in the FCR-suitable population. The EAG notes that in NICE TA689 and TA663 a similar approach was taken to capping utility values despite the quality of life data collected in the corresponding trials suggesting a higher PF utility value.[9, 12]

Another potential area of concern relates to the assumption that the utility value in the PF 2L health state is the same as applied post-progression (0.6), which may not be appropriate given the large difference in mortality rate between these two health states in the model. Clarification on this was sought from the company with a request to explore scenarios where the post-progression utility value derived from the GLOW trial is used for the PF 2L health state. In the clarification response, the company again cited TA689 and TA663 where the same approach was accepted with one utility value applied for the progressed disease health state.[9, 12] *The EAG notes the consistency in approach between the relevant CLL NICE appraisals but also highlights that the model structure in the other appraisals did not include the separate PF 2L health state. Furthermore, the potential for a higher utility value for patients who are progression-free second-line compared with patients whose disease has progressed after later lines of treatment was raised as a potential limitation of the model structure in the EAG report for TA689.*[9] *To explore this uncertainty the company provided two alternative scenarios for the utility value of the post-progression health states. In scenario 1, the post-progression utility value from GLOW ([redacted]) was applied to the PF 2L health state and in scenario 2 this value was also applied to the post-progression health state. The additional analysis was provided in response to clarification (see tables 15-17). Scenario 1 is the EAG's preferred approach.*

Adverse events

The disutilties associated with AEs were applied in the first cycle of the model using the proportion of patients experiencing grade ≥3 AEs occurring in at least 5% of patients. In addition, cardiac events were included regardless of incidence. Tables 48-50 in CS document B summarise the incidence of AEs in each patient population. As disutilties are applied separately in the model, this assumes the PF value derived from EQ-5D data collected in GLOW does not capture adverse events. The disutilties and durations applied are summarised in Table 51 in CS document B based on prior TAs and other literature sources. In general, the approach used is considered appropriate.

4.2.8 Resources and costs

The costs included in the model cover three main categories: treatment-related costs, disease management costs and end-of-life costs.

Treatment-related costs

The drug acquisition and administration costs were generally handled appropriately in the model and are consistent with NICE guidance and prior NICE TAs in CLL. Drug costs per cycle were estimated based on unit costs, dose intensity, dosing regimens and patient characteristics. Unit costs were taken from the British National Formulary (BNF),[39] Monthly Index of Medical Specialities (MIMS)[40] and electronic market information tool (eMIT)[41] which are appropriate sources. A confidential patient access scheme (PAS) is in place for ibrutinib [redacted] which is applied in the model. A PAS is also available for venetoclax but the list price is used in the company's model. Patient characteristics from the corresponding trials were used for the FCR-suitable and unsuitable/high-risk populations to estimate the costs of weight/BSA-based regimens (see CS table 56 for details). Dose reductions were included using estimated dose intensities for each component of a treatment regimen except for the VenO regimen where 100% dose intensity was assumed in the absence of data. Drug wastage was included for IV regimens only in the base case analysis. The EAG's preference is for drug wastage to be included for all treatments as excluding it may underestimate costs and would be inconsistent with the preferred approach in TA689. Table 20 summarises the drug costs per cycle applied in the model.

Table 20 Drug acquisition cost per cycle (Source, Tables 58, Document B of the CS)

Treatment	Component	Cost per cycle (£)
FCR-suitable population		
I+V	Ibrutinib	[redacted] (Cycles 1 to 15)
	Venetoclax	£1,031.14 (Cycle 4) £4,458.97 (Cycles 5 to 15)
FCR	Fludarabine	£424.20 (Cycles 1-6)
	Cyclophosphamide	£79.90 (Cycles 1-6)
	Rituximab	£1,257.35 (Cycle 1) £1,571.69 (Cycles 2-6)
FCR-unsuitable and high-risk populations		
I+V	Ibrutinib	[redacted] (Cycles 1 to 15)
	Venetoclax	£995.70 (Cycle 4) £4,305.73 (Cycles 5 to 15)
O-Clb[†]	Obinutuzumab	9,399.00 (Cycle 1) £3,312.00 (Cycles 2-6)
	Chlorambucil	£40.72 (Cycles 1-6)
VenO	Venetoclax	£59.87 (Cycle 1) £2,245.06 (Cycle 2) C3 to C15: £4,789.47 (Cycles 3 to 15)
	Obinutuzumab	£9,936.00 (Cycle 1) £3,312.00 (Cycles 2-6)
Acalabrutinib	Acalabrutinib	£4,683.96 (until progression)
Ibrutinib monotherapy[†]	Ibrutinib	[redacted](until progression)

- FCR = fludarabine + cyclophosphamide + rituximab; I+V = Ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab
- [†] Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population; * Includes the confidential PAS discount for ibrutinib
- mg = milligram; All cycles comprise of 28 days

The approach to drug administration costs is consistent with that used in NICE TAs in first-line CLL. This means no administration costs were included for oral drugs and the

administration cost for IV treatments was estimated based on NHS reference cost SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance).[42]

Following progression, patients could receive a range of subsequent treatments depending on their first-line treatment. Patients start second-line treatment following a treatment-free interval (TFI) of 14 cycles, which is based on the EAG preferred approach in TA689 and is considered appropriate.[9] The approach to costing subsequent treatments is consistent with the approach to first-line treatment as described above. Duration of subsequent treatment is modelled using second-line PFS data from the ibrutinib arm of the RESONATE trial with equivalent efficacy assumed for all treatments. The distribution of treatments was informed by UK clinical expert opinion and is summarised in Table 21.

Table 21 Subsequent treatment regimens by first-line treatment option (source, Table 60, CS, document B)

Population	First-line treatment	Subsequent treatment		
		Ibrutinib monotherapy	VenR	Acalabrutinib monotherapy
FCR-suitable	I+V	[redacted]	[redacted]	[redacted]
	FCR	[redacted]	[redacted]	[redacted]
FCR-unsuitable and high-risk populations	I+V	[redacted]	[redacted]	[redacted]
	O-Clb†	[redacted]	[redacted]	[redacted]
	VenO	[redacted]	[redacted]	[redacted]
	Acalabrutinib	[redacted]	[redacted]	[redacted]
	Ibrutinib monotherapy†	[redacted]	[redacted]	[redacted]

- † Ibrutinib monotherapy is only applicable to the high-risk population; O-Clb is only applicable to the FCR-unsuitable population

FCR = fludarabine, cyclophosphamide, rituximab; I+V = ibrutinib + venetoclax; O-Clb = obinutuzumab + chlorambucil; VenO = venetoclax + obinutuzumab; VenR = venetoclax + rituximab

A potential area of concern relates to the relatively high proportion of patients who are assumed to receive a subsequent BTK inhibitor (e.g. acalabrutinib) in second-line following initial treatment with a BTK inhibitor (e.g. following I+V), as this may be unlikely to happen in practice. Clinical expert advice explained that as I+V is a fixed duration regimen there will be a treatment gap between first-line and second-line treatment meaning it would be reasonable for some patients to receive a second BTK inhibitor second-line particularly if they have experienced a good response to first-line treatment. In general, the EAG considers

the proportions assumed for subsequent treatments are reflective of UK clinical practice. However, it was noted that there is no option for patients to receive best supportive care (BSC) which may be an appropriate treatment option, particularly in the older FCR-unsuitable and high-risk populations. Clinical expert advice suggests few patients (<5%) would receive BSC at this stage of the treatment pathway in practice and therefore any bias introduced by this omission will be minimal.

Adverse event management costs were included as one-off costs applied at start of model using incidence rates and unit costs associated with the treatment of grade ≥3 adverse events. The costs applied are reasonable and consistent with other NICE TAs. As both venetoclax and obinutuzumab are associated with a risk of tumour lysis syndrome (TLS), the model also includes associated costs of TLS prophylaxis and hospitalisations. The proportion of patients incurring these costs is informed by data from GLOW and CLL14 (see CS table 66). The cost of prophylaxis and TLS treatment is consistent with the costs applied and accepted in other relevant NICE TAs.

The EAG notes that in the FCR-suitable population the proportion requiring TLS prophylaxis and treatment is derived from GLOW which resulted in 0% of patients in the I+V arm requiring treatment or prophylaxis. It is unclear why the rate in the FCR-suitable population is substantially different from the FCR-unsuitable population where 42.5% receiving I+V required prophylaxis.

Disease management costs

Disease management cost

Disease management costs were handled appropriately in the model. A micro-costing approach was taken to estimate costs associated with PF and PD health states. Resource use does not differ by population or treatment arm, which is consistent with other NICE TAs in CLL. Health state costs per cycle were estimated from UK clinical expert opinion to which unit costs were applied using NHS reference costs (2019-20).[42] The total cost per cycle was estimated to be £105.53 in the PF health state and £252.33 in PD health states. In addition, concomitant medication costs were applied to the FCR arm of the FCR-suitable population for granulocyte colony-stimulating factor (GCSF) treatment as a one-off costs of £5,584.1. Finally, end-of-life care costs were applied as a one-off cost of £7,569.34 (inflated to 2020

prices) at the point of death based on an estimate by Round, Jones and Morris 2015, which has been accepted in other NICE TAs.[43]

5 COST EFFECTIVENESS RESULTS

This section summarises the cost-effectiveness results presented in the company submission. These consider a confidential PAS prices available to the NHS for ibrutinib, but do not account for confidential prices available for venetoclax and a number of comparator and subsequent treatments. The EAG will, therefore, produce a confidential appendix that uses the relevant confidential prices based on the sources indicated in Table 22. The confidential appendix will replicate the company's deterministic and probabilistic base case for each population, as well as the scenario analysis provided. Any further analysis undertaken by the EAG (section 6.2 below) will also be covered.

Table 22 Source of prices to be used in the Confidential Appendix

Treatment	**Source of price/type of commercial arrangement**
Ibrutinib	Simple PAS - confidential price as per the company submission
Venetoclax	Simple PAS
Obinutuzumab	Simple PAS
Chlorambucil	CMU price
Acalabrutinib	Simple PAS
Rituximab	CMU prices (high, low and closest to average scenarios)
Fludarabine	Drugs and pharmaceutical eMIT price as per company submission
Cyclophosphamide	Drugs and pharmaceutical eMIT prices as per company submission
Granulocyte colony-stimulating factor (Molecule name: Filgrastim). Administered alongside FCR	CMU prices (high, low and closest to average scenarios)

5.1 Company's cost effectiveness results

The company present their base case results in section B.3.9 of their submission. For each population, they present deterministic and probabilistic results, and also present one-way deterministic sensitivity analysis and scenario analysis.

For the populations with more than one comparator (FCR-unsuitable and high-risk), the ICER and iNMB have been presented for I+V versus each individual parameter. The base case deterministic results for each population are reproduced below in Tables 23-25.

In the FCR suitable population (Table 23), I+V has an ICER of £8,277 per QALY gained versus FCR.

In the FCR-unsuitable population (Table 24), I+V dominates VenO and O-Clb, due primarily to downstream savings in subsequent treatment costs (outweighing increased first line treatments costs) driven by its improved efficacy. Compared with acalabrutinib, I+V is less costly but also slightly less effective, giving a SW quadrant ICER with cost savings of £1,546,602 per QALY forgone. The slight reduction in QALYs compared to acalabrutinib, despite the point estimate of the HR for PFS favouring I+V, is due to the observed KM data being used to model PFS for the first 15 cycles of the model for I+V whilst acalabrutinib is modelled relative to the fitted exponential parametric curve from time zero. This results in PFS being initially lower for I+V, up to 8.6 years, before the curves cross.

The results for I+V versus VenO and acalabrutinib in the high-risk population mirror those in the FCR unsuitable population due to the equal efficacy assumption applied (Table 25). With Ibrutinib assumed to have equivalent efficacy to acalabrutinib, there is a similar QALY loss for I+V versus ibrutinib as there is versus acalabrutinib, but not exactly the same due to differences in adverse event profiles. The SW quadrant ICER for I+V versus ibrutinib comes to £675,793 per QALY forgone.

The company's base case probabilistic results can be found in the company submission document. The average ICERs from the PSAs are broadly aligned with the deterministic point estimates. In the FCR suitable population, the probability of I+V being cost-effective ranges from [redacted] at willingness to pay thresholds of £20,000 and £30,000 per

QALY respectively. The corresponding probabilities of cost-effectiveness are [redacted] in the FCR unsuitable and [redacted] in the high-risk population respectively.

Table 23 Deterministic Results: FCR-suitable population (Source: Table 79, Document B of the CS)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
FCR	[redacted]	10.83	[redacted]	[redacted]	2.01	[redacted]	£8,277	[redacted]	[redacted]
I+V	[redacted]	12.84	[redacted]	-	-	-	-	-	-

FCR = fludarabine, cyclophosphamide, rituximab; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; WTP = willingness to pay

Table 24 Deterministic Results: FCR-unsuitable population (Source: Table 81, Document B of the CS)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.88	[redacted]	-	-	-	-		
VenO	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]
O-Clb	[redacted]	8.14	[redacted]	[redacted]	1.74	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,546,602) †	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

† Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Table 25 Deterministic Results: High-risk population (Source: Table 83, Document B of the CS)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.88	[redacted]	-	-	-	-		
VenO	[redacted]	9.49	[redacted]	[redacted]	0.39	[redacted]	Dominant	[redacted]	[redacted]
Ibrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£675,793)†	[redacted]	[redacted]
Acalabrutinib	[redacted]	10.32	[redacted]	[redacted]	-0.44	[redacted]	less costly, less effective (£1,546,602)†	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay ; †Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

5.2 Company's sensitivity analyses

The company present the results of one-way sensitivity analysis in the form of tornado diagrams for I+V against each comparator in each population. These present the iNMB for I+V (at WTP of £30,000 per QALY) for the lower and upper bound of the 15 most influential input parameters.

In the FCR suitable population, the iNMB is most sensitive, in descending order, to 1) variation in the PFS hazard ratio for I+V versus FCR, 2) the extrapolation parameters of the FCR reference curve, and 3) the drug costs of I+V.

In the FCR unsuitable population, the iNMB is most sensitive to the utility value for the PF 2L and PPS state in the O-Clb comparison, and the HRs for PFS in the VenO and acalabrutinib comparisons. Similarly, in the comparison with ibrutinib in the high-risk group, the iNMB is also most sensitivity to the PFS HR for I+V versus ibrutinib.

In addition to the one-way sensitivity analysis presented, the company have undertaken a series of scenario analyses in each population. These are described and presented in section B.3.10 of their submission document. Furthermore, the EAG requested a number of additional scenarios to address further uncertainties identified at the clarification stage. For completeness, these are replicated by the EAG in chapter 6 below, along with several other scenarios explored by EAG.

5.3 Model validation and face validity check

The company describe their own steps to validate and test the consistency of their model in section B.3.13 of their submission document.

The EAG agrees in principle with the company's rationale for choosing a semi-Markov cohort model based on the requirements of the decision problem. However, the approach to populating the model still relies on extrapolating from immature PFS data, and approximating transition probabilities to progressive disease by subtracting pre-progression mortality (capped by general population mortality) from extrapolated PFS. As discussed in section 4.2.6, this leads to some inconsistencies with respect to inferred cure proportions in the FCR-unsuitable cohort but not the FCR suitable cohort where general population mortality is lower (resulting in a longer ongoing risk of progression). The EAG acknowledges the current data limitations for informing the individual transition probabilities in the model directly. Nevertheless, the plausibility of the inferred cure fractions should be further scrutinised, and the EAG believes that scenarios should at least be explored retain risks of progression over the full time horizon of the model (from PF 1L).

With respect to the long-term survival projections of their model, the company note that specific parametric curves fitted to PFS KM data (to inform transition probabilities) were validated by clinical experts at an advisory board. With respect to the Markov model projections of overall survival, the company have compared these to the Kaplan Meier based estimates of overall survival for relevant cohorts in the relevant clinical trials: the CAPTIVATE FD cohort and the FCR arm of E1912 (median 70 months follow-up) for the FCR-suitable population; and the GLOW (median 34.1 month follow-up) CLL14 (median 52.4 months follow-up) and ELEVATE-TN (median 46.9 months follow-up) trials for the FCR-unsuitable population (see Figures 45 and 46 in the company submission).

The EAG is satisfied that the model projections look generally consistent with the observed data in the FCR-suitable cohort, but note the observed follow up period is relatively short for I+V.

In the FCR-unsuitable cohort, the projections are again broadly consistent with the observed data, but OS looks to be somewhat overestimated for VenO and acalabrutinib compared to

the available observed follow-up data. In response to the clarification letter, the company also noted that the modelled separation in OS between VenO and O-Clb is consistent with recent five-year follow-up data from the CLL14 trial,[44] and that [redacted]. *They further note that clinical experts expect an OS benefit to emerge in favour of acalabrutinib versus O-Clb, consistent with the company's modelling projections (see company response to Clarification question B8 for detail).*

The company has also documented its own quality assurance/validation of the Excel model implementation, including checking of inputs, formulas, VBA code, worksheet links and cell references, undertaking a search for common errors, and conducting extreme value sensitivity analysis.

The EAG has conducted its own checks of the inputs and followed these through the engine calculations and into the results worksheets. The EAG identifies no clear errors in the programming, but notes a few minor inconsistencies as follows:

1. *The referencing of first line treatment acquisition/administration costs results in costs being applied from cycle 1 rather than cycle zero, which allows a small proportion to discontinue treatment before incurring any costs. This is similar to applying the cycle drug cost to all those who remain on treatment at the end of each model cycle. It would seem more intuitive to apply the costs to all those on treatment at the start of each cycle, but the impact on the overall cost stream will be small.*
2. *The EAG was unable to fully replicate the results for a number of scenarios supplied by the company in response to the clarification letter. These mostly related to the O-Clb arm of the model in the FCR-unsuitable population. The results for this arm presented in the clarification letter response from the company were inconsistent with those presented in the main submission document. The EAG assumes that they have been produced in error with an inappropriate setting inadvertently selected for the O-Clb arm. Therefore, the EAG has reproduced these scenarios with what it believes to be the correct settings in Chapter 6 below.*

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG asked the company to provide a number of further scenario analyses at the clarification stage to address several uncertainties as discussed in the relevant sections of chapter 4 (above). The company provided these, and a few more, in their response to the clarification letter. These scenarios are summarised below with the results replicated in section 6.2. As indicated in 5.3 above, the EAG have aligned the settings of the O-Clb arm of the model to be consistent with the results reported in the main company submission for the additional scenarios provided by the company at the clarification stage. In addition, the EAG has added a number of further scenario analyses of its own to address further uncertainties identified in its review of the economic case.

All populations

1. PF 1L utility capped at the age/sex matched general population norm, rather than based on the direct estimate from GLOW which results in higher utility than the general population (see section 4.2.7). This results in PF 1L utility being capped at 0.849 (age 58, 67.3% male) and 0.798 (age 71, 57.8% male) for the FCR-suitable and FCR-unsuitable population respectively. The PF 2L and post-progression health state utility value remains at 0.6 based on a 68-year-old cohort reported by Holzner et al and consistent with the post-progression value applied in TA689 and TA663.[9, 12, 38] (scenario provided by the company in response to the clarification letter, rerun by the EAG)
2. Apply the post-progression utility value derived from GLOW to the PF 2L state in the model, whilst retaining the lower value derived from Holzner et al. for the PPS state (see section 4.2.7).[38] With age adjustment this equates to PF 2L utility of [redacted] in the FCR suitable population, and [redacted] in the FCR-unsuitable and high-risk population. (Scenario provided by the company in response to the clarification letter, rerun by the EAG)
3. Apply the post-progression utility value derived from GLOW to the PF 2L and the PPS state in the model: [redacted] in the FCR suitable population, and [redacted] in

the FCR-unsuitable and high-risk population. (Scenario provided by the company in response to the clarification letter, rerun by the EAG)

4. PF 1L utility capped at age/sex matched general population norms with PF 2L utility applied as a relative reduction based on data from GLOW ([redacted])
5. Vary the efficacy of VenR versus ibrutinib and acalabrutinib as a subsequent treatment at PF 2L (see section 4.2.6), using a hazard ratio of:
    a. 0.5 (favouring VenR)
    b. 1.5 (favouring ibrutinib)

    (Scenario provided by the company in response to the clarification letter, rerun by the EAG)
6. Referencing of cycle specific 1st line treatment acquisition and admin costs, and treatment administration utility decrements, from cycle zero rather than cycle one (section 5.3).
7. Capping mortality and PFS using general population mortality (see section 4.2.6), inflated using a standardised mortality ratio of:
    a. 1.19
    b. 2

    (Scenario provided by the company in response to the clarification letter, rerun by the EAG)

FCR-suitable population

8. Exponential reference curve fitted directly to the PFS data of the CAPTIVATE FD cohort (see section 4.2.6), with FCR modelled relative to this using the HR form the indirect IPTW analysis ([redacted]). (Scenario provided by the company in response to the clarification letter, rerun by the EAG)
9. Linear waning of the treatment effect for I+V versus FCR from a HR of [redacted] to 1 from (see section 4.2.6):
    a. Five years after stopping treatment to 15 years after stopping treatment
    b. Five years after stopping treatment to 10 years after stopping treatment
    c. Ten years after stopping treatment to twenty years after stopping treatment

    (Scenario provided by the company in response to the clarification letter, rerun by the EAG)

FCR-unsuitable population

8. Efficacy of acalabrutinib set equal to that of I+V; HR=1 rather than [redacted]
9. Linear waning of the relative reduction in efficacy of VenO versus I+V from a HR of [redacted] to 1 from:
    a. Five years after stopping I+V treatment to 15 years after stopping I+V treatment
    b. Five years after stopping treatment to 10 years after stopping treatment
10. Cap the cycle transition probabilities of progression for all comparators in the FCR-unsuitable population, so that they cannot fall below those in the FCR suitable population – retains an ongoing risk of progression over the time horizon of the model.

High-risk population

8. Efficacy of acalabrutinib and ibrutinib set equal to that of I+V; HR=1 rather than [redacted]
9. Linear waning of the relative reduction in efficacy of VenO versus I+V from a HR of 2.00 to 1 from:
    a. Five years after stopping I+V treatment to 15 years after stopping I+V treatment
    b. Five years after stopping treatment to 10 years after stopping treatment
10. Cap the cycle transition probabilities of progression for all comparators in the high-risk population, so that they cannot fall below those in the FCR suitable population – retains an ongoing risk of progression over the time horizon of the model.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Tables 26, 27 and 28 show the results of the additional scenarios described above, for the FCR suitable, FCR-unsuitable, and high-risk population respectively. These analyses do not account for confidential discounts available for venetoclax and other comparator therapies and will also be provided in a confidential appendix to inform decision making.

In the FCR-suitable population, the cost-effectiveness findings are generally robust to individual changes. The scenarios that have greatest impact on the ICER are those that wane the relative treatment effect of I+V versus FCR (Table 26, scenario 9). The more pessimistic of these scenarios push the ICER above £20,000 per QALY, but it remains below £30,000 per QALY.

In the FCR-unsuitable (Table 27) and high-risk population (Table 28), the overall pattern of results remains the same across the scenarios explored. The scenario that caps the transition probabilities of progression, so they do not fall below those in the FCR-suitable population, has the most notable impact on incremental costs and effects versus VenO and O-Clb (Tables 26 and 27, scenario 10). However, I+V continues to be dominant over VenO and O-Clb in the FCR-unsuitable population and generates favourable costs savings per QALY forgone against acalabrutinib. In the high-risk population, I+V remains dominant over VenO and generates favourable costs savings per QALY forgone against ibrutinib and acalabrutinib.

Table 26 Further scenario analysis around the company base case: FCR-suitable population

Parameter/assumptions	Company base	Scenario	Technology	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
Company base case			I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£8,277
1. PF 1L utility	[redacted]	0.849	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£8,449
2. PF 2L utility	[redacted]	[redacted]	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£9,547
3. PF and PPS utility	[redacted]	[redacted]	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£9,739
4. PF 1L utility and PF 2L utility	PF 1L util = [redacted] PF 2L util = [redacted]	PF 1L utility = 0.849 PF 2L utility = 0.849*([redacted])	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£9,687
5. Efficacy of VenR versus ibrutinib at PF 2L	HR = 1	a) HR = 0.5	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£12,272
		b) HR = 1.5	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£5,331
6. Referencing of cycle specific 1st line treatment acquisition and admin costs, and utility decrements	From model cycle one	From model cycle zero	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£8,501
7. Capping of mortality	Age/sex matched general population mortality (GPM)	SMR adjusted GPM, SMR = 1.19	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£7,134
		SMR adjusted GPM, SMR = 2	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£2,032

8. I+V PFS curve	Relative to FCR reference curve	Exponential fitted directly to CAPTIVATE FD PFS	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£8,360
9. Proportional hazards (I+V versus FCR)	No waning of HR	Linear waning to 1 from 5 to 15 years post-treatment	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£23,903
		Linear waning to 1 from 5 to 10 years post-treatment	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£29,634
		Linear waning to 1 from 10 to 20 years post-treatment	I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£16,109

2L = second line; FCR = fludarabine + cyclophosphamide + rituximab; GPM = general population mortality; HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SMR = standardised mortality ratio; VenR = venetoclax + rituximab

Table 27 Further scenario analysis around the company base case: FCR-unsuitable population

Parameter/assumptions	Company base	Scenario	Technology	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	NMB at £20,000 per QALY
Company base case			I+V	[redacted]	[redacted]				[redacted]
			O-Clb			[redacted]	[redacted]	Dominant	
			VenO					Dominant	
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)	[redacted]
1. PF 1L utility	[redacted]	0.798	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,553,062)	[redacted]
2. PF 2L utility	[redacted]	[redacted]	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,263,117)	[redacted]
3. PF 2L and PPS utility	[redacted]	[redacted]	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,240,565)	[redacted]
4. PF 1L utility and PF 2L utility		PF 1L utility = 0.798 PF 2L utility = 0.798*([redacted])	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

	PF 1L util = [redacted] PF 2L util = [redacted]		Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,285,384)	[redacted]
5. Efficacy of VenR versus ibrutinib at PF 2L	HR = 1	a) HR = 0.5	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£9,761,867)	[redacted]
		b) HR = 1.5	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,035,443)	[redacted]
6. Referencing of cycle specific 1st line treatment acquisition and admin costs, and utility decrements	From model cycle one	From model cycle zero	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,561,806)	[redacted]
7. Capping of mortality	Age/sex matched general population mortality (GPM)	SMR adjusted GPM, SMR = 1.19	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,618,337)	[redacted]
			I+V	[redacted]	[redacted]				[redacted]

		SMR adjusted GPM, SMR = 2	O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£2,050,867)	[redacted]
8. Efficacy of I+V versus acalabrutinib	HR = [redacted]	HR = 1	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,192,372)	[redacted]
9. Proportional hazards (VenO versus I+V)	No waning of HR	Linear waning to 1 from 5 to 15 years post-treatment	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)	[redacted]
		Linear waning to 1 from 5 to 10 years post-treatment	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)	[redacted]
10. TPs for progression from PF 1L in the FCR-unsuitable population.	Allowed to diminish to zero as GPM increases	Cap cycle TPs of progression in FCR-unsuitable population so they don't fall below those in the I+V arm of	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

		the FCR-suitable population.	Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,251,471)	[redacted]

2L = second line; GPM = general population mortality; HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; O-Clb = Obinutuzumab + chlorambucil; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TPs = transition probabilities; VenO = venetoclax + Obinutuzumab; VenR = venetoclax + rituximab

Table 28 Further scenario analysis around the company base case: High-risk population

Parameter/assumptions	Company base	Scenario	Technology	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	NMB
Company base case			I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£675,793)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)	[redacted]
1. PF 1L utility	[redacted]	0.798	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£678,639)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,553,062)	[redacted]
2. PF 2L utility	[redacted]	[redacted]	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£551,126)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,263,117)	[redacted]
3. PF 2L and PPS utility	[redacted]	[redacted]	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£541,224)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,240,565)	[redacted]
4. PF 1L utility and PF 2L utility	PF 1L util = [redacted] PF 2L util = [redacted]	PF 1L utility = 0.798 PF 2L utility = 0.798*([redacted])	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£560,905)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,285,384)	[redacted]
5. Efficacy of VenR versus ibrutinib at PF 2L	HR = 1	a) HR = 0.5	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£4,446,085)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£9,761,867)	[redacted]
		b) HR = 1.5	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£449,963)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,035,443)	[redacted]
6. Referencing of cycle specific 1st line treatment acquisition and admin costs, and utility decrements	From model cycle one	From model cycle zero	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£683,142)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,561,806)	[redacted]
7. Capping of mortality	Age/sex matched	SMR adjusted GPM, SMR = 1.19	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

	general population mortality (GPM)		Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£711,237)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,618,337)	[redacted]
		SMR adjusted GPM, SMR = 2	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£909,463)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£2,050,867)	[redacted]
8. Efficacy of I+V versus acalabrutinib	HR = [redacted]	HR = 1	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£519,711)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,192,372)	[redacted]
9. Proportional hazards (VenO versus I+V)	No waning of HR	Linear waning to 1 from 5 to 15 years post-treatment	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£675,793)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)	[redacted]
		Linear waning to 1 from 5 to 10 years post-treatment	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£675,793)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,546,602)	[redacted]
10. TPs for progression from PF	Allowed to diminish to	Cap cycle TPs of progression in high-	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

1L in the high-risk population.	zero as GPM increases	risk population so they don't fall below those in the I+V arm of the FCR-suitable population.	Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£509,720)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,251,471)	[redacted]

2L = second line; GPM = general population mortality; HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; O-Clb = Obinutuzumab + chlorambucil; QALY = quality-adjusted life year; SMR = standardised mortality ratio; VenO = venetoclax + Obinutuzumab; VenR = venetoclax + rituximab

6.3 EAG's preferred assumptions

Based on the uncertainties raised in chapters 4 and 5, and reflecting on the scenario analysis conducted above, the EAG prefer to include the following assumptions in their based case.

1. PF 1L utility valued capped at general population norms
2. PF 2L utility value applied as a multiplicative decrement to PF 1L utility (multiplicative decrement = [redacted] = [redacted]))
3. First line treatment acquisition and admin costs, and treatment modality utility decrements, applied from cycle zero in the model rather than cycle one in the model.
4. Inclusion of drug wastage for oral therapies, to account for potential incomplete use of unused medicine resulting from dose intensity reductions.

The cumulative impact of these changes is shown for each population in Tables 29-31. Combined, they have modest impact on the ICER for I+V versus FCR (Table 29). The overall patter of results in the FCR-unsuitable and high-risk population remains the same (Table 30 and 31, respectively).

Further to the above, the EAG considers the extrapolation of progression risks to be an area of particular uncertainty, particularly in the FCR-unsuitable and high-risk group where the risk diminishes to zero for some treatments. Therefore, the EAG has assessed the impact of applying the waning assumptions for I+V versus FCR in the FCR-suitable population relative to its modified base case, and scenario 10 (above) to the modified EAG base case in the FCR-unsuitable and high-risk populations. The results of these scenarios are presented in Tables 32, 33 and 34 respectively. Applying waning assumption for I+V versus FCR to the EAG base case (Table 32), pushes the ICER above £20,000 per QALY. Whilst QALY gains against O-Clb and VenO are reduced in the FCR-unsuitable population, I+V remains dominant over these alternatives (Table 33). Similarly, it remains dominate over VenO in the high-risk population, and cost savings per QALY forgone remain favourable against ibrutinib and acalabrutinib (Table 34).

Probabilistic analysis on the EAG base case is provided in Tables 34-36, with corresponding cost-effectiveness acceptability curves presented in Figures 15-17. It can be noted that the

average ICER for I+V versus FCR is considerably lower than the deterministic point estimate. The exact driver is unclear.

Table 29 EAG's preferred model assumptions: FCR suitable population

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY*
Company base-case		*£8,277*
1. PF 1L utility value capped at general population norms	*4.2.7*	*£8,449*
2. PF 2L utility value applied as a multiplicative decrement to PF 1L utility (multiplicative decrement = [redacted])	*4.2.7*	*£9,687*
3. First line treatment acquisition and admin costs, and treatment modality utility decrements, applied from cycle zero in the model rather than cycle one.	*5.3*	*£9,953*
4. Inclusion of drug wastage for oral therapies, to account for potential incomplete use of unused medicine resulting from dose intensity reductions.	*4.2.8*	*£11,176*

Notes: *ICER for I+V versus FCR.

Table 30 EAG's preferred model assumptions: FCR unsuitable population

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY*
Company base-case		
O-Clb		Dominant
VenO		Dominant
Acalabrutinib		less costly, less effective (£1,546,602)
1. PF 1L utility valued capped at general population norms	*4.2.7*	
O-Clb		Dominant
VenO		Dominant
Acalabrutinib		less costly, less effective (£1,553,062)
2. PF 2L utility value applied as a multiplicative decrement to PF 1L utility (multiplicative decrement = [redacted])	*4.2.7*	
O-Clb		Dominant
VenO		Dominant
Acalabrutinib		less costly, less effective (£1,285,384)
3. First line treatment acquisition and admin costs, and treatment modality utility decrements, applied from cycle zero in the model rather than cycle one.	*5.3*	
O-Clb		Dominant
VenO		Dominant
Acalabrutinib		less costly, less effective (£1,298,020)

4. Inclusion of drug wastage for oral therapies, to account for potential incomplete use of unused medicine resulting from dose intensity reductions.	*4.2.8*	
O-Clb		Dominant
VenO		Dominant
Acalabrutinib		less costly, less effective (£1,299,198)

Notes: *ICER for I+V versus each comparator

Table 31 EAG's preferred model assumptions: High-risk population

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY*
Company base-case		
VenO		Dominant
Ibrutinib		less costly, less effective (£675,793)
Acalabrutinib		less costly, less effective (£1,546,602)
1. PF 1L utility valued capped at general population norms	*4.2.7*	
VenO		Dominant
Ibrutinib		less costly, less effective (£678,639)
Acalabrutinib		less costly, less effective (£1,553,062)
2. PF 2L utility value applied as a multiplicative decrement to PF 1L utility (multiplicative decrement = [redacted]))	*4.2.7*	
VenO		Dominant
Ibrutinib		less costly, less effective (£560,905)
Acalabrutinib		less costly, less effective (£1,285,384)
3. First line treatment acquisition and admin costs, and treatment modality utility decrements, applied from cycle zero in the model rather than cycle one.	*5.3*	
VenO		Dominant
Ibrutinib		less costly, less effective (£567,005)
Acalabrutinib		less costly, less effective (£1,298,020)
4. Inclusion of drug wastage for oral therapies, to account for potential incomplete use of unused medicine resulting from dose intensity reductions.	*4.2.8*	
VenO		Dominant
Ibrutinib		less costly, less effective (£606,789)
Acalabrutinib		less costly, less effective (£1,299,198)

Table 32 Deterministic scenario analysis on the EAG base case: FCR-suitable population

Parameter/assumptions	EAG base	Scenario	Technology	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/QALY
EAG base case			I+V	[redacted]	[redacted]			
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£11,176
9. Proportional hazards (I+V versus FCR)	No waning of HR	Linear waning to 1 from 5 to 15 years post-treatment	I+V	[redacted]	[redacted]	[redacted]	[redacted]	
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£29,167
		Linear waning to 1 from 5 to 10 years post-treatment	I+V	[redacted]	[redacted]	[redacted]	[redacted]	
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£35,799
		Linear waning to 1 from 10 to 20 years post-treatment	I+V	[redacted]	[redacted]	[redacted]	[redacted]	
			FCR	[redacted]	[redacted]	[redacted]	[redacted]	£20,131

HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; FCR = fludarabine + cyclophosphamide + rituximab; QALY = quality-adjusted life year.

Table 33 Deterministic scenario analysis on the EAG base case: FCR-unsuitable population

Parameter/assumptions	EAG base	Scenario	Technology	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	NMB at
EAG base case			I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,299,198)	[redacted]
10. TPs for progression from PF 1L in the high-risk population.	Allowed to diminish to zero as GPM increases	Cap cycle TPs of progression in high-risk population so they don't fall below those in the I+V arm of the FCR-suitable population.	I+V	[redacted]	[redacted]				[redacted]
			O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,129,502)	[redacted]

HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; O-Clb = Obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + Obinutuzumab; TP = transition probability.

Table 34 Deterministic scenario analysis on the EAG base case: High-risk population

Parameter/assumptions	EAG base	Scenario	Technology	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	
EAG base case			I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£606,789)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,299,198)	[redacted]
10. TPs for progression from PF 1L in the high-risk population.	Allowed to diminish to zero as GPM increases	Cap cycle TPs of progression in high-risk population so they don't fall below those in the I+V arm of the FCR-suitable population.	I+V	[redacted]	[redacted]				[redacted]
			VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
			Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£496,071)	[redacted]
			Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,129,502)	[redacted]

HR = hazard ratio; I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; O-Clb = Obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + Obinutuzumab; TP = transition probability.

Table 35 EAG base case for FCR suitable population – average results based on PSA (1000 iterations)

Technology	Discounted costs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	Probability cost-effective (at CE threshold = £20,000)	Probability cost-effective (at CE threshold = £30,000)
I+V	[redacted]	[redacted]				[redacted]	[redacted]
FCR	[redacted]	[redacted]	[redacted]	[redacted]	£6,245	[redacted]	[redacted]

I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; FCR = fludarabine + cyclophosphamide + rituximab; QALY = quality-adjusted life year.

Table 36 EAG base case for FCR unsuitable population – average results based on PSA (1000 iterations)

Technology	Discounted costs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	Probability cost-effective (at CE threshold = £20,000)	Probability cost-effective (at CE threshold = £30,000)
I+V	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
O-Clb	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,179,262)	[redacted]	[redacted]

I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; O-Clb = Obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + Obinutuzumab

Table 37 EAG base case for High-risk population – average results based on PSA (1000 iterations)

Technology	Discounted costs	Discounted QALYs	Incremental Costs	Incremental QALYs	ICER/QALY	Probability cost-effective (at CE threshold = £20,000)	Probability cost-effective (at CE threshold = £30,000)
I+V	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£587,432)	[redacted]	[redacted]
VenO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	[redacted]	[redacted]	[redacted]	less costly, less effective (£1,232,282)	[redacted]	[redacted]

I+V = ibrutinib + venetoclax; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; VenO = venetoclax + Obinutuzumab

Figure 15 CEAC for the EAG base case – FCR suitable population

Figure 16 CEAC for the EAG base case – FCR-unsuitable population

Figure 17 CEAC for the EAG base case – High-risk population

6.4 Conclusions of the cost effectiveness section

The company have provided an appropriate overview of published cost-effectiveness studies and previous HTA submissions for treatments for CLL. The de Novo semi-Markov model provides an appropriate structure for addressing the current decision problem. The company's model addresses the cost-effectiveness of I+V versus relevant comparators in each of the three populations identified in the final scope. Deviations from the scope in terms of included comparators has been appropriately justified. The key uncertainties in the economic case relate to uncertainties in the clinical evidence base arising from the immaturity of the data for I+V and a lack of direct head-to-head comparisons with relevant comparators. This necessitates the use of hazard ratios from indirect treatment comparisons and the extrapolation of proportional hazards assumptions to estimate cost-effectiveness against most of the key comparators. Further assumptions are required regarding the comparative efficacy of subsequent treatments in the pathway (assumed equal in the base case).

Despite the uncertainties, the company have made a reasonably robust case for the cost-effectiveness of I+V as an option for previously untreated CLL, and have addressed uncertainties with sensitivity analysis. The EAG has conducted further scenarios of its own, to which the model results appear generally robust.

The case against FCR, in the FCR suitable population, is dependent on a PFS gain for I+V versus FCR, which translates into quality of life and survival benefits based on the Markov model. This seems reasonable to expect based on the findings of the indirect IPWT comparison, and the expected relationship between progression and mortality. Whist the point estimate of the PFS hazard ratio favours I+V, however, the confidence interval is quite wide and the statistical significance of the estimate is sensitive to the weighting approach. The case further relies on a constant proportional hazards assumption being applied over the duration of the model time horizon, and scenario analysis indicates that the ICER is sensitive to waning of this effect over time.

In the FCR-unsuitable population, the case against O-Clb is perhaps the most robust, as this relies directly on head-to-head PFS data from the GLOW RCT. Whilst the PFS

data for O-Clb are mature, the same cannot be said for I+V, making the magnitude of the extrapolated health benefits uncertain. Against VenO, the case for I+V is again reliant on the application of a hazard ratio derived from an indirect comparison (anchored MAIC). The hazard ratio is suggestive of a PFS benefit favouring I+V, but this did not reach statistical significance, leading to uncertainty. Further, the appropriateness of the proportional hazards assumption over the model time horizon is uncertain. Nevertheless, the results appear generally robust to scenarios exploring waning of the relative treatment effect for I+V versus VenO. The same arguments for the case against VenO also apply to this comparison in the high-risk population.

Against acalabrutinib, the case for I+V is dependent on efficacy being similar (not substantially worse), and costs lower. Given that I+V is a fixed duration treatment, and acalabrutinib involves treating to progression, similar efficacy leads to savings in treatment acquisition costs without substantial loss in QALYs or an increase in subsequent treatment costs. Based on the evidence from the indirect treatment comparison with acalabrutinib it seems reasonable to expect I+V to have similar efficacy. However, with the immaturity of the data and the lack of randomised evidence, this remains uncertain. The same arguments and uncertainties apply to the comparisons with acalabrutinib and ibrutinib in the high-risk population.

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Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 28 November 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Data, wording and formatting clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text error: Regulatory date • Section 2.3; Pg 11; Table 3 Text: "Following the preparation of the CS, CHMP (Committee for Medicinal Products Human Use) of the EMA issued a positive opinion on 23 July 2022 for ibrutinib in combination with venetoclax (I+V) for adult patients with previously untreated CLL."	Text should be changed from "23 July 2022" to "23 June 2022".	Text error, per the EMA summary of opinion.	Text amended as described
Data error: Regulatory date • Section 2.3; Pg 11; Table 3 Text: "The European Commission marketing	Date should be changed from "4th August 2022" to "2nd August 2022".	Data error, per the EMA Procedural steps taken document.	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
authorisation approval for this indication was granted on 4th August 2022."			
<u>Data error: Patient numbers</u> • Section 3.2.1; Pg 25 Text: "GLOW was conducted in 67 centres in 14 countries in Europe and North America, including [redacted] participants ([redacted] in the I+V group, [redacted] in the O-Clb group) across [redacted] centres in the UK"	The text should be changed from "including [redacted] participants ([redacted] in the I+V group, [redacted] in the O-Clb group)" to "including [redacted] participants ([redacted] in the I+V group, [redacted] in the O-Clb group)"	Data error, per TSIDEM04 on pg 610 of the GLOW CSR.	Text amended as described
• Section 3.2.1; Pg 26 Text: "Appendix D, section D.2.3 of the CS reported that GLOW was an open-label study and assessed the risk of bias of the study as "moderate" as "patients, providers and assessors	Text should be revised to include the following: ".. GLOW was, in fact, an open-label study, however, the independent review committee (IRC) who performs tumour assessment were required to be blinded to study treatment group assignment."	The additional text (pg 29 and 33 of the GLOW CSR) provides the complete picture about the potential bias for different outcomes in GLOW study considering to its design. Janssen want to note that although the study was open-label the endpoints (PFS,	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
were not blinded". In contrast, Document B, Table 14 reports a response of 'Yes' to the question 'Were the care providers, participants and outcome assessors blind to treatment allocation'. GLOW was, in fact, an open-label study."		response) had blinded assessment and therefore reducing potential bias.	
<u>Data error: Efficacy</u> • Section 3.2.2; Table 9; Pg 36 Text: "4.7 (89.6, 97.3)" in "DOR – INV - Rate at 24 months, % (95% CI)" row and "I+V, all treated (N=159)"	The data should be changed from "4.7 (89.6, 97.3)" to "94.7 (89.6, 97.3)".	Data error, per pg 94 of the CAPTIVATE CSR.	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Data error: TEAEs of clinical interest</u> • Section 3.2.4; Table 12; Pg 46 Text: "Median follow-up: CAPTIVATE FD, 27.9 months; GLOW, median 27.9 months" in footnote	The median follow-up reported for the GLOW safety analysis should be changed from "27.9" to "27.7".	Data error, per pg 84 and 117 of the GLOW CSR.	Text amended as described
<u>Data error: Treatment-emergent adverse events (TEAEs)</u> • Section 3.2.4; Pg 47 Text: "The most reported TEAE in participants treated with I+V was diarrhoea (63.3% in CAPTIVATE FD, 50.9% in GLOW I+V arm)"	The data should be changed from "63.3%" to "62.3%".	Data error, per pg 131 of the CAPTIVATE CSR.	Text amended as described
<u>Missing data: Summary of TEAEs</u>	Data for the following additional AEs should be added from GLOW that meet the criteria for inclusion in this table (incidence in any group ≥20% for any	There are additional AEs in CAPTIVATE/GLOW that meet the	For GLOW, hyperuricaemia data is available in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 3.2.4; Table 13; Pg 49-50	grade events or ≥2% for grade ≥3 events). • Per the EMA Assessment Report (pg 85-86; pg 87): ○ Pneumonia ○ Anaemia ○ Rash ○ Neutrophil count decreased ○ Atrial fibrillation ○ TLS ○ Hyponatraemia • Per GLOW CSR (and Table 46 of Company Appendix) – to be marked as AiC: [redacted] Data for the following additional AEs should be added from CAPTIVATE that meet the criteria for inclusion in this table, per the CAPTIVATE CSR (and Table 44 of Company Appendix) – to be marked as AiC:	criteria for inclusion in this table and should be included for completeness.	the EMA assessment report and thus publicly available. Asthenia and cardiac failure are not marked as AiC further to a comment in the confidentiality marking section of this report requesting its removal. Otherwise, the text has been amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	[redacted] Lastly please also remove the data for "[redacted]" since these do not meet the criteria for reporting (incidence in any group ≥20% for any grade events or ≥2% for grade ≥3 events). "		
<u>Missing data: Summary of TEAEs</u> • Section 3.2.4; Table 13; Pg 49-50 Text: "NR"	Data could be inputted for certain cells currently showing as NR.	Data is reported in the following sources for certain table cells showing as NR: • <u>EMA Assessment Report</u> (pg 85-86) o Arthralgia from GLOW o Fatigue from GLOW o Headache from GLOW • GLOW CSR (to be marked as AiC) o [redacted]	The data for arthralgia in GLOW are not consistently reported; in the GLOW CSR (Table TSFAE02), any grade arthralgia is reported in 12 and 7 participants in the I+V and OClb groups, respectively. The EMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			assessment reports 15 and 8 participants, respectively. Data from the GLOW CSR has been added to Table 13 as this was the predominant source of data throughout the EAG report. Muscle spasms data for GLOW are reported in the EMA assessment report and thus publicly available. The remaining cells have been amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Data error: Summary of TEAEs • Section 3.2.4; Table 13; Pg 49 Text: "13 (2.4)" in "Diarrhoea" row and "GLOW O-Clb" "Any grade" column	The data should be changed from "13 (2.4%)" to "13 (12.4%)".	Data error, per Table 46 on pg 254 of the Company Appendix	Text amended as described
Data error: Summary of TEAEs • Section 3.2.4; Table 13; Pg 49 Text: "0 (0)" in "Vomiting" row and "GLOW I+V" "Any grade" column	The data should be changed from "0 (0)" to "1 (0.9%)".	Data error, per pg 85 of the EMA Assessment Report and pg 266 of the GLOW CSR	Text amended as described
Data error: Summary of TEAEs • Section 3.2.4; Table 13; Pg 50 Text: "[redacted]" in "Investigations" row and "CAPTIVATE I+V" "Grade ≥3" column	The data should be changed from "[redacted]" to "[redacted]".	Data error, per pg 253 of Company Appendix and pg 694 of CSR	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Data error: Summary of TEAEs • Section 3.2.4; Table 13; Pg 50 Text: "Eye disorders," "Renal and urinary disorders" and "Hepatobiliary disorders" table rows	These rows should be removed from the table.	None of the reported AEs meet the table criteria (incidence in any group ≥20% for any grade events or ≥2% for grade ≥3 events).	Text amended as described
Data error: TEAEs of clinical interest • Section 3.2.4; Table 14; Pg 51 Text: "1 (0.6)" in "Grade ≥3 treatment-emergent major haemorrhagic event" row and "CAPTIVATE FD I+V column"	The data should be changed from "1 (0.6)" to "2 (1.3)".	Data error, per Table 14.3.1.12.1 on pg 1,602 of the CAPTIVATE CSR.	Text amended as described
Data error: TEAEs of clinical interest	For Anaemia in I+V from GLOW, the data should be changed from "12 (11.3)" to "19 (17.9)".	Data error, per TSFAE29 on pg 452 of the GLOW CSR.	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 3.2.4; Table 14; Pg 51 Text: “12 (11.3)” and “28 (26.7)” in “Anaemia” row and “GLOW I+V” and “GLOW O-Clb” columns, respectively	For Anaemia in O-Clb from GLOW, the data should be changed from “28 (26.7)” to “19 (18.1)”.		
<u>Text error: TEAEs of clinical interest</u> • Section 3.2.4; Table 14; Pg 51 Text: “[b]Table TSFAE26 of CS: Septic shock” in table footnote	“CS” should be changed to “CSR”.	Table TSFAE26 appears in the clinical study report (CSR), rather than the company submission (CS). This should be corrected to avoid confusion.	Text amended as described
<u>Formatting error: I+V vs. VenO</u> • Section 3.4; Pg 54 Text: • Age 1 ECOG PS • CIRS score	All four items in the list (Age, ECOG PS, CIRS score, TP53 mut status) should be formatted consistently as bullets.	Formatting change for clarity.	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
2 TP53mut status			
<u>Data error: I+V vs. acalabrutinib MAIC</u> • Section 3.4; Pg 57 Text: "For the time period >12 months, the HR was [redacted], indicating a trend towards a better outcome with I+V than with acalabrutinib."	The sentence should be changed from "the HR was [redacted], indicating…" to "the HR was [redacted] after applying the ELEVATE-TN exclusion criteria and matching of four characteristics, indicating…".	The correct adjusted HR should be presented (per pg 224 of the Company Appendix). Three analyses were conducted, so clarification on which analysis is presented should be added.	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text clarification: Conclusions • Section 3.6; Pg 60 Text: "The FD cohort of CAPTIVATE, a single arm trial with an extended follow-up of 38.7 months informed the ITCs"	The word "ITCs" should be changed to singular "ITC". A similar sentence should be added related to GLOW: "The I+V arm of GLOW with an extended follow-up of 34.1 months informed the MAICs"	These clarifications should be made to make it clear that: • One ITC and two MAICs were conducted • CAPTIVATE informed the ITC only and GLOW informed the two MAICs	Text amended as described
Text clarification: Conclusions • Section 3.6; Pg 60 Text: "The GLOW trial compared I+V to O-Clb and demonstrated significant advantage of I+V over O-Clb in PFS and MRD negative rate but not for ORR, OS and majority of the quality-of-life scores in the extended follow-up (median 34.1 months) analysis."	The text should be amended as follows (with modifications in red text): "The GLOW trial compared I+V to O-Clb and demonstrated significant advantage of I+V over O-Clb in PFS, CR rate, TTNT, and MRD negative rate but not for ORR~~,~~ or OS ~~and majority of the quality-of-life scores~~ in the extended follow-up (median 34.1 months) analysis. There was no significant difference between I+V and O-Clb in [redacted] quality of life scores in the primary analysis (median 27.7 months) despite the longer duration of I+V treatment.	Significant differences in CR rate and TTNT were also observed in the extended follow-up (median 34.1 months) analysis, per pg 71 and 773 of the GLOW CSR. Quality-of-life scores were only reported in the primary analysis of GLOW and most are not published at this time. No additional assessment of PRO measures was performed after the primary analysis, per pg 81 of the GLOW CSR. It must be noted in context of QoL that treatment durations were not equal between the treatments.	Text amended as described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Data error: I+V vs. Acala MAIC • Section 4.2.6; Pg 77 Text: "*The point estimate of the HR for I+V versus acalabrutinib is close to one ([redacted])*"	The data should be changed from "[redacted]" to "[redacted]".	Data error, per Table 41 on pg 149 of Document B of the Company Submission.	Text amended as requested
Missing word: Utilities • Section 4.2.7; Pg 79 Text: "Table 18 Pre-progression utility from GLOW vs. age-adjusted general population utility (adapted from Tables 46 and 47, Document B of the CS)"	Table title should be revised to include the red text in the following: "Table 18 Pre- and post-progression utility from GLOW vs. age-adjusted general population utility (adapted from Tables 46 and 47, Document B of the CS)"	Post-progression utility included in Table 18.	Text amended as requested
Incorrect word: Utilities • Section 4.2.7; Pg 81; Table 19	Text should be changed from "FCR-suitable/high-risk" to "FCR-unsuitable/high-risk".	The corresponding columns of the table are relevant to the FCR-***unsuitable*** population, not the FCR-***suitable***.	Text amended as requested

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: “FCR-suitable/high-risk” in table header row			
<u>Incorrect abbreviation: Patient population</u> • Section 6.1; Pg 93 Text: “This results in PF 1L utility being capped at 0.849 (age 58, 67.3% male) and 0.798 (age 71, 57.8% male) for the FRC-suitable and FCR-unsuitable population respectively.”	The text should be changed from “FRC-suitable” to “FCR-suitable”.	Spelling error, the correct abbreviation for fludarabine + cyclophosphamide + rituximab is “FCR”.	Text amended as requested
<u>Missing table column label: Additional EAG scenarios</u> • Section 6.2; Pg 99; Table 27	The last (left-hand) column of the table is missing a column label. The missing text (likely NMB) should be inserted in the empty cell.	The final column of the table is missing a label.	Column header added as requested (NMB at £20,000 per QALY)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect word: Patient population • Section 6.4; Pg 117 Text: "The case against FCR, in the FCR unsuitable population, is dependent on a PFS gain for I+V versus FCR, which translates into quality of life and survival benefits based on the Markov model. "	Text should be changed from "in the FCR unsuitable population" to "in the FCR suitable population".	The paragraph discusses the population which includes FCR as a comparator, which is the *FCR suitable* population.	Text amended as requested

Issue 2 Model input clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
I+V vs. FCR ITC HR • Section 3.4; Pg 54 Text: "*The EAG notes that the ATC HR has been used in the economic modelling,*	The text should be revised to include explanation of why the ATC HR was used in the economic modelling: "The ATC analysis in which the CAPTIVATE FD cohort is matched to E1912 FCR group for all treated patients was considered as the base case in the economic modelling, given	The reasoning for using the ATC HR in the model is discussed later in the modelling section of the Company Submission (on pg 130), rather than in the earlier section on the ITC. This was because the reasoning	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
but it is not immediately clear why this choice has been made." Explanation to be added to report	that PFS with FCR from the E1912 trial is used as the reference curve in the model."	cannot be fully understood until the reference curve and PFS extrapolations in the FCR-suitable population are presented in the modelling section implying ATC as the most appropriate method for the situation.	
<u>TLS prophylaxis and treatment in the model</u> • Section 4.2.8; Pg 86 Text: *The EAG notes that in the FCR-suitable population the proportion requiring TLS prophylaxis and treatment is derived from GLOW which resulted in 0% of patients in the I+V arm requiring treatment or prophylaxis. It is unclear why the rate in the FCR-suitable population is substantially different from the FCR-unsuitable population where 42.5%*	The following explanation of this issue can be added: "Using the same criteria for GLOW and CAPTIVATE would result in 17.6% requiring treatment or prophylaxis in the I+V arm of the FCR-suitable population. The company will update this in their model."	Different definitions of requiring TLS prophylaxis and treatment were used when deriving the data used in the model for CAPTIVATE and GLOW. For CAPTIVATE, 0% was used based on the proportion of patients with high TLS risk after ibrutinib lead-in. For GLOW, 42.5% was used based on the proportion of patients with an indication for hospitalisation (based on assessment as high or medium TLS risk) after ibrutinib lead-in.	This is not really a factual inaccuracy. It is the expressed opinion of the EAG that the reason was unclear based on the evidence submitted in the company submission. We are happy to consider this update at technical engagement.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
receiving I+V required prophylaxis. Explanation to be added to report		When requiring TLS prophylaxis and treatment is defined as patients with an indication for hospitalisation after ibrutinib lead-in (per definition used for GLOW), 17.6% should be used for CAPTIVATE (per pg 65 of the EMA Assessment Report).	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 19 January 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Janssen-Cilag Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Contents

Tables and Figures

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Key issues

Janssen welcomes the opportunity to discuss the below four key issues, as well as provide additional information and updated analyses, which are provided in an appendix document as a supplement to this main response form. Janssen has also provided new analyses for the first two key issues and rationale and context for the final two key issues. Janssen has provided updated data cuts which provide additional length of follow-up for both CAPTIVATE (phase II) and GLOW (phase III) – which reduce the uncertainty of the treatment effect of I+V in the long term. Janssen has also sought clinical expert opinion to further support assumptions made in the analysis and conducted scenario analyses to explore the impact of using alternative values proposed by the EAG. The conclusion of the scenario analyses remains unchanged from the base case of Janssen's original submission, i.e. I+V is a cost-effective use of NHS resources.		
Key issue	**Does this response contain new evidence, data or analyses?**	**Response**
Key issue 1: Immaturity of progression-free survival (PFS) and overall survival (OS) data	Yes	The EAG noted that the median survival time was not reached for most of the outcomes (especially for the I+V arm of the trial) due to the immature nature of the data, which consequentially could mean increasing uncertainty. Janssen would stipulate that given **median survival time has not been reached, it indicates a lack of events over a median of 4 years of follow-up, which in turn implies that the treatment is efficacious**.

		Janssen also notes that **median PFS was also not reached in the VenO (TA663) and acalabrutinib (TA689) submissions**, indicating that similar uncertainty was observed. (1, 2) Furthermore, an **additional year of data has become available** for the phase II and III trials respectively, CAPTIVATE ([redacted] months vs 38.7 months) and GLOW (46 months vs 34.1 months). **Figure 1** and Figure 3 below present a comparison of the PFS Kaplan Meier (KM) data between the original and updated data-cuts from CAPTIVATE and GLOW. **Figure 2 and**

		Figure 4 present a comparison of the OS KM data between the original and updated data-cuts from CAPTIVATE and GLOW. The additional length of follow-up data from CAPTIVATE and GLOW provides more mature PFS and OS data which **reduces the uncertainty of the treatment effect of I+V in the long term**. **Figure 1: CAPTIVATE FD no del17p cohort – Comparison of PFS KM data from original (38.7m) and updated ([redacted]) data cuts**

		 **Figure 2 CAPTIVATE FD no del17p cohort – Comparison of OS KM data from original (38.7m) and updated ([redacted]) data cuts**

		 **Figure 3: GLOW – Comparison of PFS KM data from original (34.1m) and updated (46m) data cuts**

		 **Figure 4: GLOW – Comparison of OS KM data from original (34.1m) and updated (46m) data cuts**

Table 1 and Table 2 present the PFS rates from CAPTIVATE FD and the hazard ratio (HR) for I+V vs chlorambucil + obinutuzumab (O-Clb) from GLOW from the original and updated data cuts respectively. The outcomes are consistent with longer follow-up data hence indicating a **consistency in the treatment effect of I+V in the long term.**

Table 1: CAPTIVATE FD no del17p cohort – Comparison of PFS rates from original (38.7m) and updated ( ) data cuts

I+V follow-up	Non-del17p PFS (INV) at 36m	Non-del17p PFS (INV) at m
37.8m	89.1%	N/A

Table 2: GLOW – Comparison of HR of I+V vs O-Clb from original (34.1m) and updated (46m) data cuts

	Original data cut	Updated data cut
HR of I+V vs O-Clb from GLOW (IRC-assessed)	HR 0.21 95% CI: 0.13, 0.35; p<0.0001	0.20 95% CI: 0.13, 0.32, p<0.0001

IRC: Independent review committee

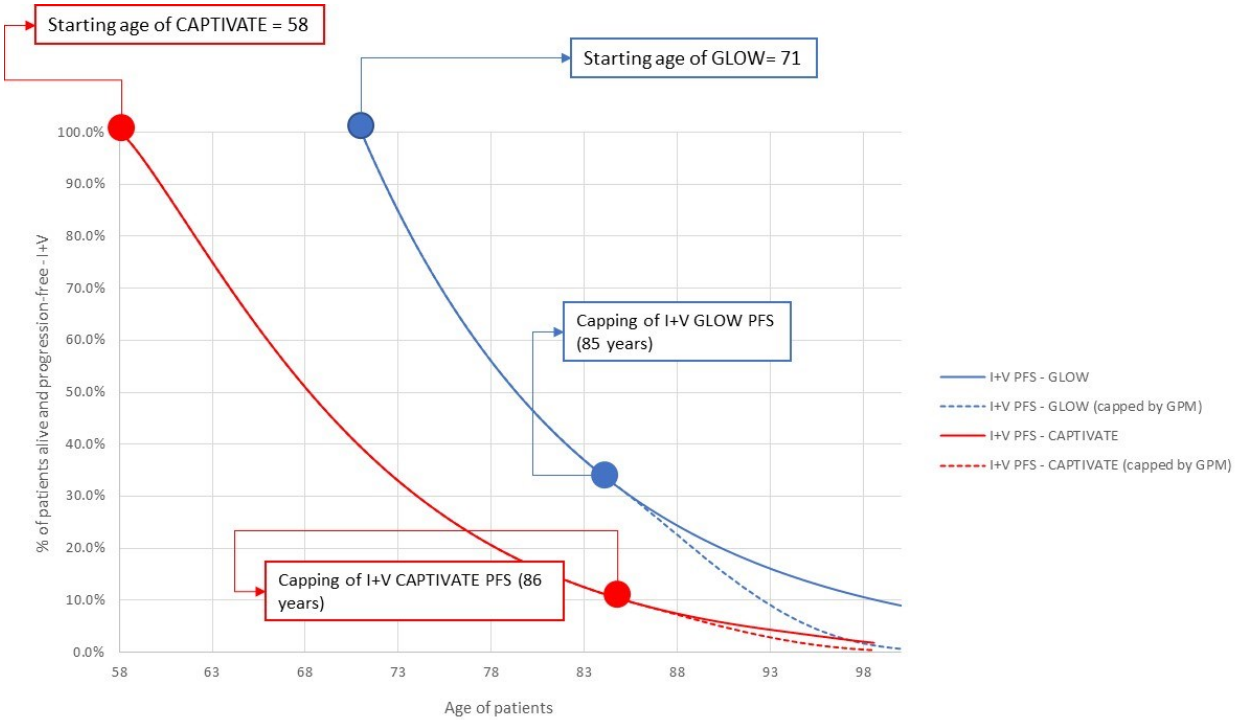
Key issue 2: Further justification is needed on the implicit assumption that at a certain time point, a proportion of patients essentially face a zero risk of further progression and a mortality rate in line with age/sex matched general population	Yes	In the FCR-unsuitable population, at a certain time point, a proportion of patients essentially face a zero risk of further progression and a mortality rate in line with age/sex matched general population. The EAG note that this infers a cure for a fraction of the FCR-unsuitable population. The EAG highlight that this is a less obvious problem in the younger FCR-suitable population where the background mortality for the age-sex matched general population is lower, resulting in the extrapolated risks of progression or death remaining higher than the general population over the majority of the modelled time horizon. Thus, the risk of progression remains non-zero for longer. The EAG note that this is inconsistent across populations. Janssen wish to highlight that the **age at which mortality is capped by general population mortality (GPM) is consistent across both the FCR-suitable and FCR-unsuitable cohorts, i.e., around 85/86 years.** Figure 5 shows the I+V PFS hazards of the FCR-suitable population, where capping happens when patients are ~86 years old. Figure 6 shows the I+V PFS hazards of FCR-unsuitable/high-risk population, where capping happens when patients are ~85 years old.

		Figure 5: PFS hazards of I+V in the FCR-suitable population capped by GPM 

Figure 6: PFS hazards of I+V in the FCR-unsuitable population capped by GPM

Figure 7 shows the capping of PFS curves by GPM for both the populations. Capping occurs when the solid lines (uncapped curves) start to deviate from the dotted lines (capped curves). The graph shows that regardless of the starting age in the FCR-suitable and FCR-unsuitable cohorts, capping with GPM occurs around the same age.

Figure 7: PFS hazards of I+V in the FCR-suitable and FCR-unsuitable populations capped by GPM



Furthermore, Janssen has sought clinical expert opinion on the clinical plausibility that patients treated with targeted agents at first-line (1L) and reached remission and were 85+ years, are more likely to die than

		progress.(3) Clinicians have indeed validated this is in line with their expectations; **at that advanced age, death (from CLL or other causes) rather than progression is the most likely event.** These insights are presented in the Appendix.(3) Nonetheless, given that some patients may still progress rather than die even at that advanced age, the EAG had implemented a scenario in their model where the risk of progression in the FCR-unsuitable population is capped by the PFS hazard in the FCR-suitable population. Janssen has replicated that scenario in its own model and wishes to highlight this is a conservative analysis as patients are now accruing second-line (2L) costs and experiencing a lower quality of life compared to the base case, whereby they have a higher quality of life in 1L and die, thus accruing no costs in 2L. Under that scenario, I+V remains dominant vs fixed-duration treatments O-Clb and VenO; and I+V is cost-saving vs continuous treatments acalabrutinib and ibrutinib demonstrating that **irrespective of scenario related to risk of progression I+V remains a cost-effective use of resources.**

Key issue 3: The progression-free utility value applied in the model lacks face validity	No	Janssen contends that the progression-free utility value sourced from GLOW has face validity, based on the rationale provided below. This is an evidence-based input in the economic model, with the evidence derived from the most robust source, i.e., the phase III randomised clinical trial GLOW. Furthermore, **efficacy data is derived from GLOW and therefore for consistency**, it is methodologically appropriate for the **utility value to be derived from the same trial.** **Three large and independent phase III trials, GLOW, CLL14 and ELEVATE-TN from different sponsors have all yielded EQ-5D scores which are higher than general population utility**.(1, 2, 4) This may be due to the fact that patient-reported outcomes in general are reliant on patients' relative assessment of their wellbeing. Individuals from the general population would be expected to have roughly the same quality of life from day to day; however, a CLL patient who previously suffered from severe fatigue and started a treatment which alleviated the fatigue and provided relief from symptoms would report a much higher quality of life the next day. Therefore, it is plausible that patients may report a progression-free utility which is higher than their general population counterparts. Patients included in the GLOW trial appropriately represented the population of CLL patients who are unsuitable for fludarabine-based CIT but are likely to tolerate less-intense treatment with O-Clb, based on age (≥65 years) or CIRS score >6 and CrCl <70 mL/min. The median patient age in GLOW was 71.0 years, which is similar to the median age of CLL diagnosis reported in England (72 years).(5, 6) Therefore, the HRQoL of patients from GLOW would accurately represent the target population who would likely be treated in clinical practice and should therefore be representative of the HRQoL of that cohort. The fact that 3 trials which enrolled patients at different timepoints (CLL14 in 2014, ELEVATE-TN in 2015 and GLOW in 2018) and have different designs all while being carried out by different sponsors/trialists but

		have yielded similar utility values, implies that the utility values themselves are not a result of selection bias.(1, 2, 4) The **utility values from these 3 separate trials result in a strong evidence base**, which needs to be acknowledged and factored into decision making. Any assertion on face validity is inherently subjective and based on the expectation that mean patient utility should be lower than general population norms. There are other areas for example Ara and Brazier (2009) that show mean patient utility exceeding general population norms in cardiovascular disease (CVD): for ages above 75, the average utility tariff of those with no CVD (but they may have other conditions) is lower than the average utility of those with at least one CVD condition.(7) Nonetheless, Janssen has **explored scenarios** in which utility values were based on the age and gender adjusted general population values to **explore the impact of alternative utility values**, in line with EAG's preferred assumptions. The detailed results are presented in Table 14. The ICER of I+V vs FCR in the FCR-suitable population increased compared with the base case but remained under the £20,000 per QALY threshold. In the FCR-unsuitable and high-risk populations, the total QALYs and incremental QALYs gained by I+V decreased slightly, but overall, the ICER findings did not change from the base case results; **I+V remains a cost-effective use of resources.**

Key issue 4: Applying the same utility value to the progression-free (PF) 2L and post-progression survival (PPS) health states may not be reflective of patients' quality of life after progressing on first-line treatment	No	In the base case analysis, a utility for the PPS health state was derived from Holzner et al.,(8) which reported a utility of 0.6 (age = 68) for 2L and all other post-progression states by applying age-adjustment. Janssen's positioning is that it is a reasonable approach, given that this approach was previously used in TA689 and TA663, where only a single utility value (0.60) was applied for the entire 'progressed disease' state, and accepted by the Committee.(1, 2) Nonetheless, at the EAG's request, Janssen has conducted scenario analyses in which alternative values for the post-progression states were evaluated. At clarification stage, Janssen provided two scenarios in which a more conservative **value of** [redacted] **derived from GLOW was applied to PF 2L** in one scenario, and also to PPS after 2L PFS in a second scenario. The conclusion of the scenario analyses was unchanged from the base case of the submission, i.e. **I+V remains a cost-effective use of NHS resources**. In line with EAG's preferred assumptions, Janssen has also conducted a further scenario analysis where the PF 1L utility is capped at age/sex matched general population norms and PF 2L utility is applied as a relative reduction based on data from GLOW [=[redacted]]. The results from this scenario are presented in more detail in Table 14. The ICER of I+V vs FCR in the FCR-suitable population increased compared with the base case but remained under the £20,000 per QALY threshold. In the FCR-unsuitable and high-risk populations, the total QALYs and incremental QALYs gained by I+V decreased slightly, but overall, the ICER findings did not change from the base case results; **I+V remains a cost-effective use of resources.**

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Additional issues from the EAR

Janssen is grateful for the opportunity to discuss the below additional issues. Janssen has provided further evidence to support assumptions made in the analysis, sought clinical expert opinion as validation for clinical assumptions, conducted scenario analyses to explore the impact of alternative assumptions or values, and made changes to the cost-effectiveness model to incorporate exploratory scenarios at EAG's request. The conclusion from all the scenario analyses and exploratory analyses conducted are unchanged from the base case of Janssen's original submission, indicating that results of the analysis are robust and I+V is a cost-effective use of resources.			
Issue from the EAR	**Relevant section(s) and/or page(s)**	**Does this response contain new evidence, data or analyses?**	**Response**
Additional issue 1: Assuming equivalent efficacy between the FCR-unsuitable population and the high-risk population may not capture the poorer prognosis	Section 4.2.6, Page 78	Yes	Janssen wishes to present new evidence to further support the assumption of equivalent efficacy between the FCR-unsuitable and high-risk populations. A published pooled analysis by Allan *et al.* (2022) presents long-term efficacy data for 89 CLL patients with del17p and/or TP53 mutations, who are treated with 1L ibrutinib-based therapy.(9) The pooled analysis includes patients from across four studies.(9) Figure 8 shows that the PFS curves for the I+V arm of the FCR-unsuitable population [black curve] and the arm for the pooled del17p/TP53 patients from four 1L trials [blue curve] are relatively aligned.(9) This supports the current model assumption that these patient groups have similar prognosis and hence, the assumption of equivalent efficacy between the FCR-unsuitable population and high-risk population has face validity. This is a large, pooled, multi-study data set which is very informative given CLL is an orphan disease,

of a high-risk population			and only 10% of patients have del17p and/or TP53 mutations. **Figure 8: PFS curves in the high-risk population**  The arm for the pooled del17p/TP53 patients from four first-line trials [blue curve] has a younger population compared to the I+V arm of the FCR-unsuitable population [black curve]. The median age in the blue curve cohort is 65 years vs 71 years in the black curve cohort, and the proportion of patients aged 65 years or older is 52% vs 85% in the black curve cohort (Table 3). These differences in baseline characteristics may help explain why the prognosis of the blue curve may be better and trending higher than the black curve. The graph indicates that it is unlikely that an assumption of equivalent efficacy between the FCR-unsuitable and high-risk populations would not capture the poor prognosis of a high-risk population.

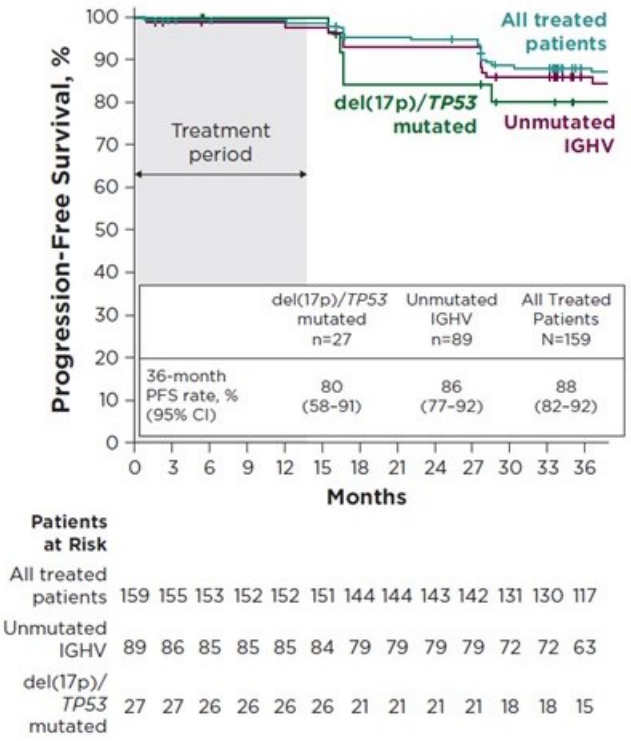
Table 3: Overview of baseline characteristics from I+V arm of GLOW and arm for the pooled del17p/TP53 subgroups from four 1L trials

Trial	GLOW	Pooled analysis
Treatment	I+V	Ibrutinib ± anti-CD20 antibody
Patients, n	n=106	n=89
Median years (range)	71.0 (47, 93)	65 (33, 87)
Age≥65 years	85%	52%
Male, n (%)	59 (55.7)	61 (69)
Bulky disease ≥5 cm, n/N (%)	41/105 (39.0)	33/88 (38)
TP53 mutation, n (%)	7 (6.6)	53* (91)
del17p, n (%)	0 (0)	47 (53)
Unmutated	55 (51.9)	60† (69)

* TP53 sequencing results available for 58 patients
† Data available for 87 patients

Additional issue 2: An analysis of a subgroup of patients with IGHV unmutated CLL should be considered if possible	Section 4.2.6, Page 58	Yes	IGHV mutation status is not routinely tested in the UK and therefore does not impact treatment decisions. Janssen had discussed this in the company submission (CS) as part of the decision problem; IGHV test results are not required by NICE or Cancer Drugs Fund (CDF) criteria to receive a specific treatment in first line CLL and ibrutinib is efficacious independent of IGHV status;(10) therefore, the results in the FCR-suitable and FCR unsuitable populations are more representative of UK clinical practice than in populations determined by IGHV mutation status. In the EAG report, the EAG agreed with Janssen's position. Therefore, whilst information about outcomes for patients with different IGHV mutation status may be interesting from an academic point of view, it should have no bearing on the reimbursement decisions of CLL patients in the UK. Nonetheless, at EAG's request, Janssen has provided the context and results from an exploration of considering IGHV mutation status as a treatment effect modifier in the FCR-suitable and FCR-unsuitable population. <u>FCR-suitable population</u> In the FCR-suitable population results from CAPTIVATE FD cohort did not suggest a difference in PFS between the ITT and unmutated IGHV patients' subgroup (Figure 9).(11) In the indirect comparison with FCR, the IGHV status was taken into account when weighting the populations, therefore no further adjustments would be needed.

Figure 9: PFS of CAPTIVATE FD Cohort (39m) for ITT and by IGHV and High-Risk Status



Due to rapid enrolment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.

FCR-unsuitable population

1. **Evidence from phase III study GLOW suggests that the effect of I+V was not substantially different between patients with mutated and unmutated IGHV.**

PFS HRs of I+V vs O-Clb in the unmutated and mutated IGHV subgroups suggested that the effect of I+V in both subgroups is similar to each other and to that of ITT population.(6) Therefore, results of the

ITT population were considered representative regardless of IGHV status.

Table 4 GLOW PFS (IRC) Outcomes of I+V vs O-Clb for ITT and by IGHV subgroup

Population	I+V	O-Clb	PFS (IRC) HR (95% CI)
ITT	106	105	0.216 (0.131 – 0.357)
Unmutated IGHV	55	54	0.269 (0.148 – 0.488)
Mutated IGHV	27	27	0.233 (0.065 – 0.839)

CI: confidence interval; O-Clb: chlorambucil + obinutuzumab; HR: hazard ratio; IGHV: immunoglobulin heavy-chain variable gene region; I+V: ibrutinib + venetoclax; IRC: independent review committee-assessed; ITT: intention-to-treat; PFS: progression-free survival

2. **Determining the relative effect of I+V compared to other treatments in a subgroup of unmutated IGHV patients only would be challenging as noted by EAG.**

This would be mainly due to:

- The small sample size of such patients in GLOW study (n=55 for I+V and n=54 for O-Clb).(6) Furthermore, the differences in baseline characteristics between the GLOW and CLL14 cohorts would mean that matching would be challenging for the matched-adjusted indirect comparison (MAIC), therefore leading to a very small effective sample size and consequently, considerable uncertainty.
- There are no baseline characteristics available for a subgroup of unmutated IGHV patients only for outside-trial comparators (VenO and acalabrutinib) which means a strong assumption of equal baseline characteristics between ITT and unmutated IGHV populations in the comparator studies would need to be applied – hence adding more uncertainty.

Given these considerations it is unlikely that the results from this scenario would result in reliable outcomes for decision-making.

3. **Nonetheless, at the EAG's request, IGHV mutation status was included in the MAICs informing the FCR-unsuitable population as an exploratory scenario.**

The results of the MAICs for I+V vs VenO and acalabrutinib in the FCR-unsuitable population when IGHV mutation status is excluded (Base Case) and included (exploratory scenario) are presented in Table 5. The results suggest that when IGHV mutation status is factored into the MAIC, the PFS HRs

<table>
<tr>
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<td></td>
<td>improve slightly in favour of I+V vs VenO and become more similar to acalabrutinib.

Table 5 MAIC results for PFS (INV) of I+V (GLOW; 46m) vs VenO (CLL14, 40m) and Acalabrutinib (ELEVATE-TN; 47m) in FCR-unsuitable patients including (Base Case) and excluding (scenario analysis) IGHV status from matching
<table>
<tr><th>Population</th><th>Base Case PFS (INV)
HR (95% CI)</th><th>Base Case + IGHV PFS (INV)
HR (95% CI)</th></tr>
<tr><td>I+V vs VenO</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>I+V vs Acalabrutinib</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
CI: confidence interval; HR: hazard ratio; IGHV: immunoglobulin heavy-chain variable gene region; INV: investigator-assessed; I+V: ibrutinib+venetoclax; m: months; PFS: progression-free survival; VenO: venetoclax+obinutuzumab</td>
</tr>
<tr>
<td>Additional issue 3:

Issues around the extrapolation of immature data and violation of proportionality assumption of the survival analyses further increase the uncertainty around the estimates presented.

The potential impact of these effects waning over time has not been explored in the</td>
<td>Section 3.6, Page 60

Section 4.2.6, Page 77</td>
<td>Yes</td>
<td>As discussed previously, in the original submission, Janssen presented a median follow-up of 38.7 months of CAPTIVATE data and 34.1 months of GLOW data.(12, 13) Janssen is now submitting a median follow-up of [redacted] months of CAPTIVATE FD cohort data and 46 months of GLOW data.(14-16) The additional length of follow-up data from CAPTIVATE and GLOW provides more mature PFS and OS data which reduces the uncertainty of the treatment effect of I+V in the long term.

The longer follow-up data has been incorporated into analyses of the indirect treatment comparison (ITC) vs. FCR, the MAIC vs. VenO and the MAIC vs. acalabrutinib. The ITC results have remained consistent, showing outcomes in favour of I+V vs FCR and VenO (Table 6 and

Table 7). This indicates a consistency in the treatment effect of I+V in the long term.

Table 6: I+V vs. FCR PFS HR from original and updated CAPTIVATE FD data cuts
<table>
<tr><th></th><th colspan="2">ATC HR (95% CI), p-value</th></tr>
<tr><th></th><th>Original data cut</th><th>Updated data cut</th></tr>
<tr><td>All treated patients without del17p excluding any with missing covariate values</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
ATC: average treatment effect in the control population</td>
</tr>
</table>

FCR-unsuitable population

Table 7: I+V vs VenO and acalabrutinib MAIC Results Summary for original and updated GLOW data cuts

	VenO		Acalabrutinib	
	Base Case HR (95% CI)		Base Case HR (95% CI)	
	Original data cut	Updated data cut	Original data cut	Updated data cut
PFS(INV)	[redacted]	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]	[redacted]
TTNT	[redacted]	[redacted]		

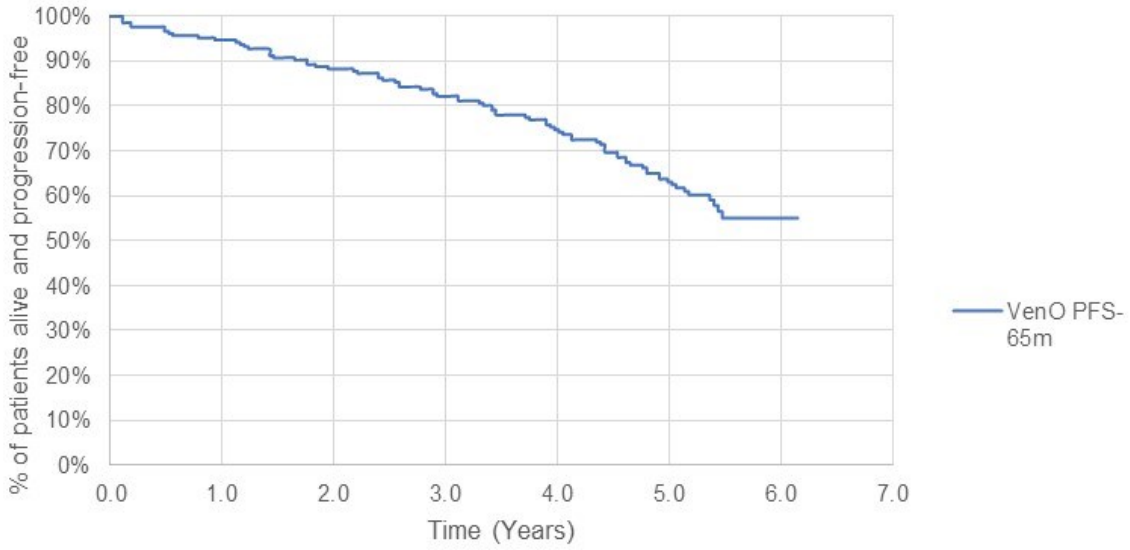
CI: confidence interval; HR: hazard ratio; I+V: ibrutinib + venetoclax; INV: investigator; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment; VenO: venetoclax + obinutuzumab

Probabilistic sensitivity analysis addresses the uncertainty from the confidence interval of the HR for the FCR-unsuitable population, and cost-effectiveness acceptability curves indicate that I+V is the most cost-effective treatment in this patient population at a willingness-to-pay threshold of £30,000.

In addition, pessimistic treatment waning scenarios were added to the FCR-unsuitable population, similar to the analyses provided previously for the FCR-suitable population to vary the assumptions of proportional hazards over a lifetime. The scenarios accounted for a “waned” I+V arm which is generated by applying a HR versus the reference I+V curve.

When treatment waning is applied, the reference I+V curve approaches the “waned” I+V arm in the treatment waning period. The scenarios aligned with the results for the FCR suitable population and included linear waning applied to I+V and VenO for:

- 5 years post-treatment and takes 5 years to achieve equal benefit
- 5 years post-treatment and takes 10 years to achieve equal benefit
- 10 years post-treatment and takes 10 years to achieve equal benefit

			I+V remains dominant vs O-Clb and VenO and is cost-saving vs acalabrutinib in the FCR-unsuitable population for these scenario analyses. **The conclusion from these scenario analyses remains unchanged from the base case; I+V remains a cost-effective use of resources.** Figure 10 shows the PFS KM curve of VenO from the latest CLL14 data cut. The fact that there is no sudden change in the shape of the curve indicates that there is no treatment waning effect. The shape of the curve beyond 5 years of follow-up data should be interpreted with caution, due to the very low number of patients at risk at that point. Given that both VenO and I+V are FD targeted agent combinations which include venetoclax, the expectation would be that I+V would follow the same trend, i.e., there would be no treatment waning in the long-term. **Figure 10: Observed VenO PFS in CLL14 (65m datacut)** 

Additional issue 4: When a parametric curve was fitted directly to the PFS data of the CAPTIVATE FD cohort, the choice of an exponential parametric curve, guided only by the observation that PFS in the younger/fitter FCR-suitable population should be higher (no worse) than in the FCR-unsuitable population, is not very well justified	Section 4.2.6, Page 66	No	PFS KM data from the CAPTIVATE FD cohort is not used directly in the model to estimate long-term survival extrapolations due to scarcity of PFS events. At clarification stage, Janssen provided a scenario where a parametric curve was fitted directly to the PFS data of the CAPTIVATE FD cohort. EAG notes that the exponential distribution chosen for that extrapolation seems to be guided only by the assumption that PFS in the FCR-suitable population should be higher (no worse) than the FCR-unsuitable population and notes that the assumption is not very well justified. Different parametric fits were applied to CAPTIVATE FD KM data to generate long-term survival estimates. A HR of I+V vs FCR was then applied to these curves to generate corresponding FCR curves. The choice of exponential distribution was guided by the visual fit and clinical plausibility of landmark estimates of patients alive and progression-free in the FCR arm yielded by the extrapolations, when compared to external data from ECOG1912. Figure 11 presents the parametric fits to FCR curves, generated from HR applied to I+V CAPTIVATE FD KM. Figure 11 shows that exponential and log-normal provide the best visual fits.

Figure 11: Parametric fits to FCR curve generated from HR applied to I+V CAPTIVATE FD KM

Table 8 below illustrates that exponential and log-normal both provide landmark estimates of the proportion of patients alive and progression-free which align with long-term estimates from external data from ECOG1912.

Table 8: Comparison of proportion of patients alive and progression-free at landmark timepoints between extrapolations of parametric fits and external data from ECOG1912

Distribution	1-year	2-year	5-year	6-year	10-year	15-year	20-year	30-year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			<table><tr><td>Gamma</td><td>[redacted]</td></tr><tr><td>Gompertz</td><td>[redacted]</td></tr><tr><td>ECOG1912</td><td>5-year PFS:50% 6-year PFS: 43.1%</td></tr></table> The visual fit and landmark estimates conclude that both exponential and log-normal distributions are plausible candidates for the parametric fit to CAPTIVATE FD PFS data. However, when log-normal is fitted to CAPTIVATE FD PFS KM data, it yields a median PFS of [redacted] months which is close to the median PFS of I+V from GLOW ([redacted] months). Janssen sought clinical expert opinion on the expectation that the PFS in the younger/fitter FCR-suitable population should be higher (no worse) than in the FCR-unsuitable population. Clinicians validated that they would expect a younger/fitter patient to have a better outcome than an elderly/unfit patient if treated with the same regimen.(3) This insight is presented in the Appendix.
Additional issue 5: Adding in third-line (3L) treatment costs to the analysis, to align with RESONATE trial efficacy data and current clinical practice	Section 4.2.6, Page 72	Yes	At the EAG's request, Janssen has updated the cost-effectiveness model to incorporate 3L treatment costs to the analysis. In order to apply 3L treatment costs to the analysis, 3 inputs are needed: 1. Proportion of patients eligible to receive 3L treatment 2. Distribution of treatments received at 3L 3. Costs of treatments received at 3L <u>Proportion of patients eligible to receive 3L treatment</u> Janssen has sought clinical expert opinion on the proportion of patients expected to receive treatment at 3L, if they are treated with targeted agents at 1L and 2L. A clinical expert indicated that that the proportion receiving subsequent treatment was 30%. This is in line with the RESONATE data in which 19.6% of patients in the 1-2 prior treatment line subgroup of ibrutinib arm received 3L CLL therapy. Clinicians also discussed that the reason for patients not receiving 3L treatment may be a myriad of reasons including frailty, competing co-morbidity, lack of desire of having ongoing therapy, death from causes other than CLL. Other clinicians mentioned 100% of patients would receive 3L therapy. It was noted that some patients would be enrolled in clinical trials and therefore would not receive regimens funded by the NHS. These insights are presented in the Appendix.(3) <u>Distribution of treatments received at 3L</u> Janssen has evaluated the RESONATE trial data which indicates that 18 patients received a subsequent CLL treatment after progression from treatment with ibrutinib in the 1-2 prior-line subgroup

(Table 9). Only therapies which were received by more than 1 patient and no experimental treatment were factored in the analysis; as such, only venetoclax-based (assumed as venetoclax + rituximab), idelalisib-based (assumed as idelalisib + rituximab) regimens and antibody therapy (assumed as rituximab) were included in the analysis. Janssen then used this data to inform the distribution of CLL treatments received at 3L (Table 10). Given the small sample size, the results from the analysis need to be interpreted with caution. Janssen also sought clinical opinion on the distribution of treatments received at 3L and most clinicians indicated most patients would receive a venetoclax-based regimen. These insights are presented in the Appendix.(3)

Three scenario analyses were conducted based on the RESONATE trial 1-2 prior line ibrutinib arm and clinician feedback:

a. 20% of patients receive 3L CLL treatment and the distribution of subsequent treatments is based on RESONATE 1-2 prior lines sub-group of ibrutinib arm (Table 10)
b. 100% of patients receive 3L CLL treatment and the distribution of subsequent treatments is based on RESONATE 1-2 prior lines sub-group of ibrutinib arm (Table 10)
c. 100% of patients receive 3L CLL treatment and they all receive a venetoclax-based regimen (assumed as venetoclax + rituximab)

Table 9: Subsequent therapy received for CLL by patients who had 1-2 prior treatments from ibrutinib arm of RESONATE, implemented in the cost-effectiveness model

Subsequent therapy received for CLL	**Proportion of patients receiving**
Proportion receiving subsequent treatment	19.6%
Composition of subsequent treatment	**Number of patients receiving**
Venetoclax-based	7
Idelalisib-based	3
Antibody therapy	3
Ibrutinib	1
Experimental treatment	3
Transplant	1
Total	18

Table 10: 3L therapy distribution sourced from patients who had 1-2 prior treatments from ibrutinib arm of RESONATE, implemented in the cost-effectiveness model

Subsequent therapy received for CLL	**Proportion of patients receiving**
Venetoclax + rituximab (VenR)	53.8%

Idelalisib + rituximab (Id+R)	23.1%
Rituximab	23.1%

Costs of treatments received at 3L

A one-off cost was calculated based on the drug acquisition cost, dosing regimen and treatment duration.

This one-off cost was applied to 20% and 100% of patients eligible to receive CLL treatment at 3L, based on RESONATE data and feedback from the clinical experts (Appendix). This **has minimal impact on the ICER,** as the cost is applied to a very low number of patients.

Additionally, Table 11 shows that most patients spend minimal time in the progressed disease (PD) health state for all populations, and as such, the impact on the ICER is minimal. Patients who spend longest in PD are patients on O-Clb and FCR, and will therefore accrue the most costs, making the ICER more in favour of I+V.

Table 11: Total LYs and PPS LYs (Discounted) in the model

Comparator	Total LYs	PF 2L LYs	PD LYs
FCR-suitable population			
I+V	12.97	3.20	3.57
FCR	10.84	4.67	5.23
FCR-unsuitable population			
I+V	9.52	1.58	1.73
O-Clb	7.94	5.10	5.64
VenO	9.24	3.03	3.32
Acalabrutinib	9.66	2.11	2.31
High-risk population			
I+V	9.52	1.58	1.73
VenO	9.24	3.03	3.32
Acalabrutinib	9.66	2.11	2.31
Ibrutinib	9.66	2.11	2.31

Additional issue 6: Scenario analysis around the choice of parametric function for O-Clb arm in FCR-unsuitable population	Section 4.2.6, Page 72-73	Yes	Janssen conducted scenario analyses around the choice of parametric fits for the O-Clb arm in the FCR-unsuitable population. The alternative parametric fits explored were: 1) Weibull which matches the observed data well 2) log-normal and log-logistic which provide a more optimistic extrapolation for O-Clb and fits the observed data relatively well, 3) exponential which provide the most optimistic extrapolation for O-Clb in the long-term but underestimates the observed data in the trial. The conclusion from the scenario analyses remains unchanged from the base case, i.e. **I+V remains dominant vs O-Clb**, thus showing that results are consistent and are robust to more optimistic curves for the comparator. These results are presented in more detail in the appendix document submitted as a supplement to this main response form.

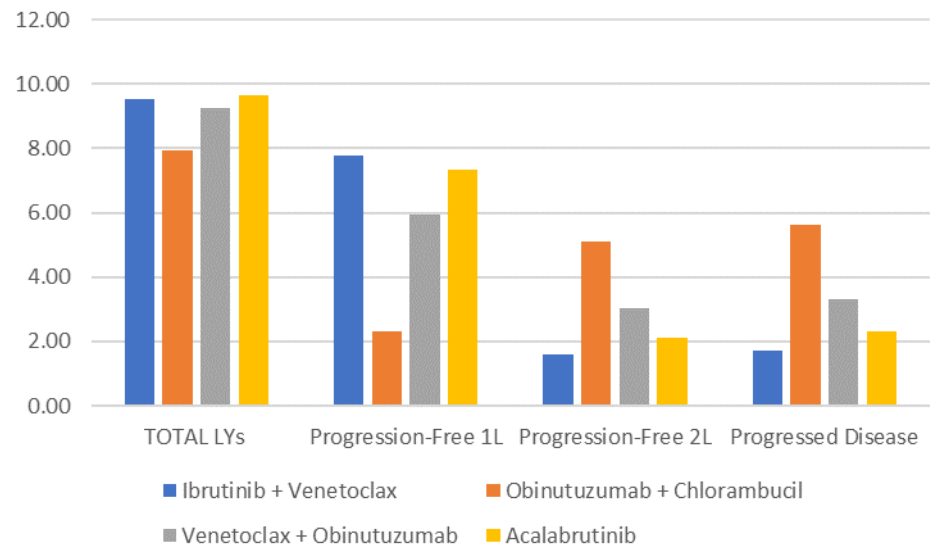
<table>
<tr>
<td>Additional issue 7:

The PFS outlook is substantially better in the second line for those who receive O-Clb at first line in the FCR-unsuitable population</td>
<td>Section 4.2.6, Page 77</td>
<td>No</td>
<td>Compared to patients receiving targeted treatments, patients in the O-Clb arm face a higher progression hazard at 1L. This means that patients progress quicker after receiving O-Clb at 1L compared to I+V, VenO or acalabrutinib and end up spending longer in 2L receiving a Bruton’s tyrosine kinase inhibitor (BTKi) or venetoclax-based treatment. Janssen sought clinical expert opinion on this, and clinicians confirmed that they would expect patients receiving O-Clb at 1L to progress quicker and spend longer in 2L, compared to patients receiving targeted agents at 1L.(3) This insight is presented in the Appendix.

Table 12 shows the discounted life years (LYs) accrued by patients split across the different health states for all comparators in the FCR-unsuitable population. The graph shows that patients on O-Clb spend the shortest time in progression-free (PF) 1L health state (2.30 LYs) but the longest in PF 2L and PD states (5.10 and 5.64 LYs) compared to targeted agents. Figure 12 further illustrates this.

Table 12: Discounted LYs by comparator in FCR-unsuitable population

<table>
<tr><th>Comparator</th><th>Total LYs</th><th>PF 1L</th><th>PF 2L LYs</th><th>PD LYs</th></tr>
<tr><td>I+V</td><td>9.52</td><td>7.79</td><td>1.58</td><td>1.73</td></tr>
<tr><td>O-Clb</td><td>7.94</td><td>2.30</td><td>5.10</td><td>5.64</td></tr>
<tr><td>VenO</td><td>9.24</td><td>5.92</td><td>3.03</td><td>3.32</td></tr>
<tr><td>Acalabrutinib</td><td>9.66</td><td>7.35</td><td>2.11</td><td>2.31</td></tr>
</table>
PF: progression-free; PD: progressed disease</td>
</tr>
</table>

			Figure 12: Discounted LYs by comparator in FCR-unsuitable population 
Additional issue 8: The proportion of patients requiring tumour lysis syndrome (TLS) prophylaxis or treatment was 0% in the FCR-suitable population	Section 4.2.8, Page 86	Yes	Janssen had previously sourced the proportion of patients requiring TLS prophylaxis or treatment for CAPTIVATE FD from a corresponding table to GLOW. However, upon reviewing the data in more detail, Janssen can now confirm that the proportion of patients eligible for TLS prophylaxis or treatment from CAPTIVATE FD should be 17.6% (per page 65 of the EMA Assessment Report). (17) Janssen had previously sourced the proportion of patients requiring TLS prophylaxis from the GLOW CSR – 24 out of 69 patients who were classified to be high-risk TLS patients at baseline were no longer considered to be high-risk after 3 cycles of ibrutinib lead-in (as per page 260). However, there are some patients who have missing information. In order to account for this, the proportion of patients in the I+V arm who are at a high risk of TLS in the FCR-unsuitable and high-risk population should be 46.2% (per page 261 of the GLOW CSR) which is a more conservative estimate of TLS risk after ibrutinib lead-in. Janssen had previously reported that the proportion of patients experiencing TLS emergent events in the VenO arm to be 13.4%. This was incorrect and should be 1.4% as 3 out of 216 patients receiving VenO in the CLL14 trial experienced TLS hospitalization. This new input was implemented in the model as part of the revised base case and **the impact on the**

			ICER is minimal (Table 13**).**

Janssen has collated additional issues in the below table, for which no new analysis was needed and has provided further context and clarification for each.

Additional issue	Relevant section(s) and/or page(s)	Clarifications
The incidence of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuations was lower in CAPTIVATE FD compared to the I+V arm of GLOW despite these two groups having the same treatment duration	Section 3.2.4, Page 46-47	Janssen has sought clinical expert opinion on the clinical plausibility of elderly/unfit patients experiencing a higher incidence of TEAEs, including compared to young/fit patients, if both groups of patients receive the same treatment. Clinicians agreed that this is indeed in line with their expectations, as elderly/unfit patients are more likely to have co-morbidities, which increase the risk of TEAEs – regardless of the treatment administered.(3) This insight is presented in the Appendix. Furthermore, it is important to note that the cohorts for the FCR-suitable and FCR-unsuitable populations are considerably different in terms of baseline characteristics (age, stage of advanced disease, renal function etc) and therefore have different prognosis. As such, comparison of outcomes across trials with different populations should be made with caution.
Double counting of disutility	Section 4.2.7, Page 80	Janssen notes there is not double counting of disutility based on the approach used and has provided further explanation on the implementation below. While the IV disutility for each component is applied additively, the total IV disutility per cycle for a treatment regimen is calculated as the minimum of the disutility associated with individual components. For example, in FCR, Fludarabine and cyclophosphamide are infused 3 times per cycle from cycle 1-6 and hence are associated with a disutility of -0.12, whereas rituximab is infused only once per cycle and is associated with a disutility of -0.04. The disutility of FCR per cycle is the minimum of three values (-0.12 (fludarabine), -0.12 (cyclophosphamide), and -0.04 (rituximab)) and hence is -0.12. This does not result in any double counting.
There is no option for patients to receive best supportive care (BSC) which may be an appropriate treatment option, particularly in the older FCR-unsuitable and high-risk populations	Section 4.2.8, Page 85	Janssen agrees that few patients (<5%) would receive BSC at this stage of the treatment pathway in practice and therefore any bias introduced by this omission will be minimal. Furthermore, given the cost of BSC drugs such as prednisolone is relatively inexpensive, this would have a minimal impact on the ICER. Finally, these patients still accrue costs associated with routine care in the

		model, i.e., costs for laboratory tests, healthcare professional visits, tests associated with disease monitoring etc.
Inconsistencies in results for O-Clb arm in FCR-unsuitable population between original CS and clarification	Section 5.3, Page 92	Janssen can confirm that the scenarios ran by the EAG in the review document are accurate. The results in Janssen's clarification response had been produced in error with an inappropriate setting inadvertently selected for the O-Clb arm

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 13: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made during technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 1: Immaturity of PFS and OS data	CAPTIVATE median follow-up: 38.7 months GLOW median follow-up: 34.1 months	CAPTIVATE median follow-up: [redacted] months GLOW median follow-up: 46 months	These revised ICERs are based on the updated data cuts and updated ITCs/MAICs implemented in the model FCR-suitable population: • Base case before TE: £8,277 • Base case after TE: £3,083 = -£5,194 FCR-unsuitable population: • Base case before TE: o I+V vs O-Clb: Dominant o I+V vs VenO: Dominant o I+V vs acalabrutinib: Less costly, less effective (£1,546,602)†

			• Base case after TE:
			  ○ I+V vs O-Clb: Dominant
			  ○ I+V vs VenO: Dominant
			  ○ I+V vs acalabrutinib: Dominant
			High-risk population:
			• Base case before TE:
			  ○ I+V vs VenO: Dominant
			  ○ I+V vs acalabrutinib: Less costly, less effective (£1,546,602)†
			  ○ I+V vs ibrutinib: Less costly, less effective (£675,793)†
			• Base case after TE:
			  ○ I+V vs VenO: Dominant
			  ○ I+V vs acalabrutinib: Dominant
			  ○ I+V vs ibrutinib: Dominant

Additional issue 8: Proportion of patients eligible for TLS prophylaxis or treatment was 0% for CAPTIVATE	Proportion of patients eligible for TLS prophylaxis or treatment from CAPTIVATE = 0%	Proportion of patients eligible for TLS prophylaxis or treatment from CAPTIVATE = 17.6%	Only the ICER for the FCR-suitable population is presented as this change only impacts this population. FCR-suitable population: • Base case before TE: £8,277 • Base case after TE: £3,395 = -£4,882

Company's base case following technical engagement (or revised base case)	Incremental QALYs: FCR-suitable population: • I+V vs FCR = [redacted] FCR-unsuitable population: • I+V vs O-Clb: [redacted] • I+V vs VenO: [redacted] • I+V vs acalabrutinib: [redacted] High-risk population: • I+V vs VenO: [redacted] • I+V vs acalabrutinib: [redacted] • I+V vs ibrutinib: [redacted]	Incremental costs: FCR-suitable population: • I+V vs FCR = [redacted] FCR-unsuitable population: • I+V vs O-Clb: [redacted] • I+V vs VenO: [redacted] • I+V vs acalabrutinib: [redacted] High-risk population: • I+V vs VenO: [redacted] • I+V vs acalabrutinib: [redacted] • I+V vs ibrutinib: [redacted]	These revised ICERs are based on the updated data cuts and updated ITCs/MAICs implemented in the model, and updating the proportion of patients eligible for TLS prophylaxis or treatment from 0% to 17.6% for CAPTIVATE FCR-suitable population: • I+V vs FCR = £3,395 FCR-unsuitable population: • I+V vs O-Clb: Dominant • I+V vs VenO: Dominant • I+V vs acalabrutinib: Dominant High-risk population: • I+V vs VenO: Dominant • I+V vs acalabrutinib: Dominant • I+V vs ibrutinib: Dominant

All ICERs presented include the patient access scheme (PAS) for Ibrutinib; † Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Sensitivity analyses around revised base case

Janssen has outlined in the table above that the revised base case comprises of implementing the updated data cuts from CAPTIVATE FD and GLOW and the resulting ITC/MAICs from this. Furthermore, the proportion patients eligible for TLS prophylaxis or treatment was for CAPTIVATE FD was updated from 0% to 17.6%. The proportion of patients who are high-risk for TLS in the I+V arm for the FCR-unsuitable and high-risk populations were derived from the GLOW CSR and updated from 42.1% to 46.2%. The proportion of patients who experience TLS hospitalizations in the VenO arm was derived from the CLL14 trial.

Below, Janssen has presented results for scenario analyses outlined throughout the document, in response to key and additional issues. All ICERs presented include PAS for Ibrutinib.

Across the scenario analyses, I+V is cost-effective or dominant vs FCR in the FCR-suitable population. I+V is dominant vs O-Clb and VenO across all scenario analyses, i.e. I+V is less costly and more effective. I+V is dominant or cost-saving vs ibrutinib monotherapy and acalabrutinib monotherapy in all scenario analyses. The conclusion from all the scenario analyses and exploratory analyses conducted are unchanged from the base case of Janssen's original submission, indicating that results of the analysis are robust and I+V is a cost-effective use of resources.

Table 14: Scenario analyses

Company's base case following technical engagement (or revised base case)	Scenario analysis	Incremental Costs	Incremental QALYs	ICER/QALY
PF 1L utility capped by general population norms				
FCR-suitable population = 0.86	PF 1L utility = 0.849	Incremental costs vs FCR: [redacted]	Incremental QALYs vs FCR: [redacted]	I+V vs FCR = £3,465
FCR-unsuitable population = 0.81	PF 1L utility = 0.798	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant
High-risk population = 0.81	PF 1L utility = 0.798	I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted] I+V vs ibrutinib: [redacted]	I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted] I+V vs ibrutinib: [redacted]	I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant I+V vs ibrutinib: Dominant
PF 1L utility capped by general population and PF 2L utility calculated via a relative multiplier of PF 1L				
FCR-suitable population = 0.86 (PF 1L) FCR-suitable population = 0.63 (PF 2L)	PF 1L utility = 0.849 PF 2L utility = [redacted]	Incremental costs vs FCR: [redacted]	Incremental QALYs vs FCR: [redacted]	I+V vs FCR = £3,980

FCR-unsuitable population = 0.81 (PF 1L) FCR-unsuitable population = 0.59 (PF 2L)	PF 1L utility = 0.798 PF 2L utility = [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Less costly, less effective (£4,004,544)†
High-risk population = 0.81 (PF 1L) High-risk population = 0.59 (PF 2L)	PF 1L utility = 0.798 PF 2L utility = [redacted]	I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted] I+V vs ibrutinib: [redacted]	I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted] I+V vs ibrutinib: [redacted]	I+V vs VenO: Dominant I+V vs acalabrutinib: Less costly, less effective (£4,004,544)† I+V vs ibrutinib: Less costly, less effective (£1,658,410)†
3L treatment costs				
No 3L treatment costs included	3L treatment costs included; 20% of patients receive 3L treatment, applied as a one-off cost (VenR = 53.8%, Rituximab = 23.1%. Id+R = 23.1%)	I+V vs FCR: [redacted]	I+V vs FCR: [redacted]	I+V vs FCR: £1,921
		I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant
		I+V vs Ibrutinib: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs Ibrutinib: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs Ibrutinib: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant
No 3L treatment costs included	3L treatment costs included; 100% of patients receive 3L treatment, applied as a one-off cost (VenR = 53.8%, Rituximab = 23.1%. Id+R = 23.1%)	I+V vs FCR: [redacted]	I+V vs FCR: [redacted]	I+V vs FCR: Dominant
		I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant

		I+V vs Ibrutinib: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs Ibrutinib: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs Ibrutinib: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant
No 3L treatment costs included	3L treatment costs included: 100% of patients receive 3L treatment, applied as a one-off cost (VenR = 100%)	I+V vs FCR: [redacted]	I+V vs FCR: [redacted]	I+V vs FCR: Dominant
		I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant
		I+V vs Ibrutinib: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs Ibrutinib: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs Ibrutinib: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Dominant
Treatment waning in FCR-unsuitable population				
No treatment waning effect included for FCR-unsuitable population	Treatment waning effect applied in FCR-unsuitable population to I+V and VenO for: 5 years post-treatment and takes 5 years to achieve equal benefit	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Less costly, less effective (£1,728,616)†
No treatment waning effect included for FCR-unsuitable population	Treatment waning effect applied in FCR-unsuitable population to I+V and VenO for: 5 years post-treatment and takes 10 years to achieve equal benefit	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Less costly, less effective (£2,912,454)†

No treatment waning effect included for FCR-unsuitable population	Treatment waning effect applied in FCR-unsuitable population to I+V and VenO for: 10 years post-treatment and takes 10 years to achieve equal benefit	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: [redacted] I+V vs VenO: [redacted] I+V vs acalabrutinib: [redacted]	I+V vs O-Clb: Dominant I+V vs VenO: Dominant I+V vs acalabrutinib: Less costly, less effective (£57,531,964)†

† Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

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Appendix

Due to the limited published data in CLL prognosis and 3L treatment distribution available for this submission, input from local clinical experts was sought in the form of interviews.(3) Interviews were conducted by Janssen in January 2023 with the following healthcare providers:

- Christopher Fegan (CF), Consultant Haematologist (retired), University Hospital of Wales, Cardiff
- Robert Ayto (RA), Consultant Haematologist, Queen Alexandra Hospital, Portsmouth
- Sunil Iyengar (SI), Consultant Haematologist Royal Marsden Hospital
- Toby Eyre (TE), Consultant Haematologist Royal Marsden Hospital

Interview questions and clinician responses are presented in the sections below.(3)

Prognosis

Question 1: If a patient is treated with a targeted agent in 1L, stays in remission and reaches 85+ years, do you think that the risk of death is higher than the risk of progression?

- Response from CF: Yes the risk of death at 85 is higher than progression, of those that die I would say it's a 50:50 split between dying of CLL and dying of something else. BTKis diminish immunoglobulins and there is evidence they don't fully return so many of these patients die of infection.
- Response from RA: It is reasonable to say there is a higher chance of death at that age.
- Response from SI: There's quite good 2L treatment so I'd expect them to respond again. But I think likely to progress, having said that at age 85 with life expectancy being less than that they are more likely to die of other causes.
- Response from TE: Patients get highly effective treatment 1L Given an average CLL diagnosis age of 72 and then by the time they get through years of treatment (probably 7 years on acalabrutinib and then 2 years on venetoclax) they will be in their 80s so yes most patients would not die of their CLL.

Question 2: Do you expect PFS of a young/fit patient to be better than that of an elderly/unfit patient when they are treated with the same treatment?

- Response from CF: Very interesting question, if you give the same therapy to two different groups of patients do you get the same response. The answer is definitely not. The reasons are not well known. The young fit would do better because they are motivated and want to live longer rather than for short term goals. I did a study locally in Cardiff and found that depravation index is a stronger marker because they tend to put the way they feel down to comorbidities rather than CLL and their compliance is worse. I would expect a 45 year old to do better than a 75 year old because the older patient is more likely to die of infections.
- Response from RA: We expect a good response to time limited treatment, and those with good prognosis CLL have a good lifespan. Patients with TP53 enrichment and complex karyotype won't do as well. Younger patients should perform a bit better due to less comorbidities. I think older patients will still respond but will suffer from more toxicity whichever treatment you give.
- Response from SI: I would expect the length of remission to be no different based on age.
- Response from TE: Yes the PFS should be better in younger fitter patients for number reasons. More likely to have competing events, and tolerability of treatment is better if younger. And less likely to discontinue due to toxicity and older patients may have inferior dose intensity.

Question 3: Do you expect a higher incidence of AEs in an elderly/unfit patient compared to a young/fit patient if treated with the same treatment?

- Response from CF: I never saw evidence that age effected the reporting of toxicity. In the RESONATE studies we didn't see the hypertension and atrial fibrillation (AF)and I'd expect that because they were more likely to tolerate drugs as their tolerance was higher. But now with other drugs providing more choice patients will ask for different drugs. It's about perception. I only had two to three patients where I had to stop treatment due to true toxicity. If you have other comorbidities that all add up to make your life a misery, average CLL patient has four other comorbidities. I think the other cumulative other factors are more important.
- Response from RA: Yes I would. This is due to older patients having poorer renal function, also bone marrow function isn't as robust, they may have more infusion reactions, and they have more AEs and therefore more dose reductions, toxicity and more treatment delays.

- Response from SI: Yes I'd expect the incidence of AEs to be higher in elderly/unfit. A number of factors come in to play, whether it is fixed or continuous treatment. Patients with comorbidities are likely to come off continuous treatment for things such as cardiac issues whereas younger patients wouldn't. And the same is likely with FD treatments.
- Response from TE: Absolutely. With any drug in the world ever. This is a consistent result from studies in CLL such as different in GLOW and CAPTIVATE in terms of toxicity. This is due to a combination of age, underlaying frailty and comorbidities.

Question 4: If a patient who received O-Clb at 1L is compared to a patient who received targeted agent at 1L, would you expect the O-Clb patient to progress quicker?

- Response from CF: Yes all the evidence suggests that.
- Response from RA: Yes

Question 5a: If we were to think about a patient to had O-Clb at 1L vs. a targeted agent at 1L, who has a higher risk of progression?

- Response from TE: I would suspect risk of progression to 2L is worse for the patients who had the targeted therapy 1L. But there is no data to go on. But if you had a patient who is progressing on acalabrutinib 1L vs. O-Clb 1L the more inferior the 1L the more likely you are respond well to a 2L therapy because that second therapy is more targeted. Looking at Murano, VenR arm would be worse in a post covalent BTKi setting because during that time they had 1 prior line which was chemotherapy. But if they have had a BTKi and become resistant to it they would do worse. So I would extrapolate that theory to 2L setting, so someone who progressed through acalabrutinib and then had VenR do not do so as well as someone who had O-Clb and then had VenR.

Question 5b: Who would you expect to progress quicker to 2L therapy? Someone who had O-Clb or someone who had targeted agent at 1L?

- Response from TE: The O-Clb will progress way earlier. The trial data is clear.

Question 5c: And then spend longer at 2L?

- Response from TE: Yes, probably.

3L treatment distribution

Question 6: What % of patients do you expect to receive treatment at 3L, if given targeted treatment at 1L and 2L?

- Response from CF: I think all of them would. Who says bendamustine + rituximab (BR) won't give a meaningful response after I+V? The mechanisms are different so might do a job for you. I saw the data for pirtobrutinib, I was underwhelmed, 18 months PFS is not a game changer for someone who is young. I think you would do just as well with BR if naive to it. BTKi resistance comes into play, there will be a role in the future for what the resistance mechanism is because some patients with some resistances will respond to other treatments such as zanubrutinib. If patient responded to FD venetoclax why not go back to it.
- Response from RA: I can always find a treatment so 100% as long as they are fit for therapy and it's appropriate. Re-challenge might be an option or a clinical trial with BTK degraders, or LOXO-305. There's very few people that get there that you can't give treatment to.
- Response from SI: Most patients will reach 3L at some point, we haven't mentioned risk different groups. Patients with unmutated IGHV and TP53 mutation will mostly reach 3rd line, whereas TP53 wild type will have longer remission periods with targeted agents. But many patients will get to 3L unless they die of other reasons. % without TP53 mutation that get to 3L, we are seeing such good remissions so it's not many, 25-33% probably and 60-70% of TP53 mutated patients will get to 3L.
- Response from TE: Younger fitter patients are more likely to get to 3L. If we think about the average age of CLL patients being at 72 and treated with acalabrutinib into remission then venetoclax at 2L they will be around 85 years old. Probably around 30% maybe 40%. Patients will have other health problems in their mid-80s which will cause death at that age. But I think you'd get 10 years of life out of the first two lines of therapy. Younger fitter patients are more likely to get to 3rd line and those with high risk disease.

Question 7: Are there any reasons why patients might not receive 3L treatment (e.g., too frail, lack of treatment options)?

- Response from CF: None.
- Response from RA: Very few people that you can't give treatment to, a small percentage some elderly patients may get some palliative treatment.

- Response from SI: Of patients who don't get to 3L it's because they are still in remission, the fact that many are elderly means they would have died of something else 3L.
- Response from TE: A combination of factors, such as frailty, competing morbidity, lack of desire to have ongoing therapy, cognitive impairment. All these make delivery more difficult. But this will depend on the type of therapy as that will make it more difficult to give, example being idelalisib who you'd give that to.

Question 8: How do you expect 3L treatment to be distributed?

- Response from CF: I have used idelalisib. But usually within 12 months the disease came back. These were heavily treated patients. The toxicity wasn't manageable long-term. Idelalisib 5-10%; clinical trials 20-25% and chemotherapy. The remainder 70% would be split between BTKi and venetoclax but also some chemotherapy. I might give them BR and try to get the clone down and then give venetoclax + rituximab (VenR). Ibrutinib 1L, then venetoclax-based regimen, how do you know that the venetoclax regimen hasn't killed the clones that were BTKi resistant. So re-challenge with BTKi might be reasonable.
- Response from RA: Depends on how the treatment is sequenced. If you had VenO, then you could rechallenge with venetoclax at 3L. If they had a BTKI first then have venetoclax that sequence is a bit more difficult because you have gone through two therapies with less options left, so would look at clinical trials with examples being with BTK degraders or pirtobrutinib. PI3ki could be tried but not predicted to have a great response. 10-15% for trials. Then venetoclax based treatment making up the rest of the proportion, or PI3ki. Would challenge with BKTi if stopped to intolerance. I would think that is all split evenly.
- Response from SI: We now have venetoclax retreatment as a 3L option. Before that option we would have used idelalisib, but its usage is coming down. We have a clinical trial open so would often put patients down that route. 3L depends on what they had 1L, if they had VenO 1L then would have BTKi 2L then have VenR 3L. If they have a BTKi 1L and then VenR 2L then venetoclax monotherapy 3L. In terms of proportion: 70% clinical trials, 15% idelalisib and 15% venetoclax monotherapy. I've had a good experience with idelalisib, I like it as it's a different type of therapy.
- Response from TE: Depends on what has been used. Probably even split between pirtobrutinib and venetoclax, and some in trials (45% venetoclax, 45% pirtobrutinib, 10% trials). And no idelalisib. I haven't used it in a long time and it's not something that's needed.

- If used a BTKi 1L then VenR 2L, you would either use a non-covalent BTKi 3L. (Pirtobrutinib will be approved within the next 12 months I think). Or to retreat with venetoclax monotherapy. I think those are the two options. Idelalisib is an option but nobody really uses that.
- If patients had VenO and then acalabrutinib then either give venetoclax or a non-covalent BTKi. So 3L Ven mostly currently, the ability to re-treat is supported by data.
- If using fixed duration BTKi + venetoclax in 1L then after that we don't know what to do for 2L. But one can assume that you could use a BTKi and Ven venetoclax, so we would probably use a BTKi continuous and then fixed venetoclax and then even another try at venetoclax at a later line. In the future we might move to genetic testing to guide treatment decision.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Clinical expert statement and technical engagement response form

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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Thank you for your time.

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NICE National Institute for Health and Care Excellence

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Part 1: Treating chronic lymphocytic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Nagesh Kalakonda
2. Name of organisation	University of Liverpool and The Clatterbridge Cancer Centre NHS Foundation Trust
3. Job title or position	Professor and Honorary Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic lymphocytic leukaemia ? ☐ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for chronic lymphocytic leukaemia ?	Prevent progression, prolong life expectancy, and improve Quality of Life. Mitigate long term side effects of treatments

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Prolongation of remission duration following treatment. The reduction in nodal disease or splenic enlargement if relevant. Normalisation of blood counts in case of pre-treatment cytopenias Significant reduction in bone marrow infiltration Achievement of deep MRD which is increasingly shown to be relevant for long term outcomes.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	Despite significant advances in the treatment of CLL and availability of non-chemotherapeutic options the disease remains incurable and patients frequently need multiple lines of therapy. At least some of the options at present contain infusional elements and some of the treatments are not of fixed duration. There is currently no established or agreed protocol for rational sequencing of novel therapies especially when used as monotherapies (with or without a monoclonal antibody). An unanswered question is whether a fixed duration treatment allows future re-use of combined or individual agents with reasonable response rates. The differences in clonal selection pressures between fixed duration vs continuous treatments and impact on disease behaviour is not clear. A fixed duration regime that combines two effective agents may be attractive for healthcare professional and patients.
11. How is chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	The current options, widely adopted in the UK, are well articulated in the BSH guideline for CLL treatment (frontline, relapsed/refractory and supportive care) and were published in 2022. My experience is UK based.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The technology will provide an additional option (of combining two active drugs) for a fixed duration and may have the potential to improve duration and depth of responses
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Both drugs are now routinely used by haemato-oncologists in hospital settings. There are no perceived obstacles or problems for the use of the combined treatment. Most centres that use such agents will have established access to diagnostic services and equipment (such molecular diagnostics, MRD assessments, flow cytometry etc.) Centres will also have support of specialist nurses and pharmacists.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The technology has the potential to 1) increase the duration of remissions after frontline treatment 2) facilitate the option of re-use for future lines of therapy 3) decrease the potential for clonal selection pressure that may contribute to more aggressive disease in the future. 4) abrogate the need for day care based infusional treatments 5) Improve quality of life of patients once the fixed duration treatment is complete There is, however, a potential for greater frequency of adverse events especially greater frequency of secondary cardiac events. It remains to be seen if such risks are less with a fixed duration treatments vs continuous BTKi therapies.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? • Would you anticipate ibrutinib plus venetoclax to be more effective in certain populations compared with others? • For example would ibrutinib with venetoclax result in a different risk of disease progression for the FCR-unsuitable compared with FCR suitable population?	Combining two effective agents that target distinct pathways in CLL for high risk patients (e.g UM-CLL and p53 aberrations) has the potential to be very effective in the long-term. A fixed duration 'oral' treatment is also attractive in elderly patients. Whilst it is likely to be very well tolerated in younger patients there is a possibility of higher incidence of treatment related adverse events necessitating dose attenuations, treatment delays and discontinuation in an older dempgraphic.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	One does not foresee any difficulties for administration or care of patients on the combination. There may be a need more frequent out-patient visits whilst on treatment. Additionally, the elimination of the need for infusions (monoclonal antibodies) will relive day ward costs and pressures.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are currently no formal or informal accepted criteria for stopping treatments is largely healthcare staff and patient driven. The treatment, if well tolerated will likely be used for the whole 'fixed' duration. Formal rules for dose attenuations, delays (especially in the face of emergent adverse events) may emerge with wider use and will be useful for physicians. Such guidance may require the input of other specialists (e.g cardiologists who may recommend additional investigations). It is unclear if there additional interventions such as immunoglobulin replacements are more likely to be needed in patients in the long term.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	The reduced burden on day ward pressure as the proposed treatment is oral may be worth considering, if not already taken into account.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	A fixed duration treatment may in the long term reduce the need for frequent OP appointments as is currently needed for continuous BTKi treatments. The potential for re-use of drugs may be a major advantage Patients may be less likely to experience clonal selection (and potentially high grade transformation). Remains to be seen if this reduces the need for transplantion or CAR-T treatments in the treatment cohorts compared to comparator treatments and regimes.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Combining two novel and effective therapies certainly makes clinical and scientific sense. In addition, a fixed duration of treatment is attractive for physicians and patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There exists the likelihood of dose delays, attenuations and more frequent hospital visits due to emergent adverse events during the treatment which may be more common compared to the use of the drugs as monotherapy. A fixed duration schedule may mitigate some of the issues mentioned above. Occasional patients may need referrals to or input from other specialists (e.g. cardiologists). Overall, one does not expect any impact on patients quality of life significantly over and above that experienced in comparator regimes within the appraisal.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The control/comparator arms within the trials that inferences are derived from have been superceded in the UK and not the current standards of care. Longer term outcomes and adverse effects remain to be established.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The ongoing UK-FLAIR trial which has recently published interim analysis is likely to provide further insights with regards to safety and efficacy.
22. **a) Do you agree with the comparator selection per population below?** **b) Which of the comparators are most relevant per population and why?** **c) Are you aware of any new evidence for the comparator treatment(s) since the publication of the following NICE technology appraisal guidance:** People without a del17p or TP53 mutation FCR suitable: • FCR (TA174) FCR un-suitable: • O-Clb (TA343) • VenO (TA663) • Acalabrutinib (TA689) People with a del17p or TP53 mutation (high-risk) • Acalabrutinib (TA689) • VenO (TA663) • Ibrutinib (TA429)	Longer term follow up of some of the comparator data have been published as abstracts or manuscripts and will likely continue to emerge.

23. How do data on real-world experience compare with the trial data?	None available for I+V
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	None foreseen

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Immaturity of overall survival (OS) and progression free survival (PFS) data • Is there additional longer-term evidence currently available that would reduce the current uncertainty resulting from the immaturity of the data? *Data is immature because of short follow up	None to my knowledge
Key issue 2: The approach to generating transition probabilities by extracting age/sex matched general	No

population mortality from extrapolated PFS, leading to diminishing risks of progression in the surviving cohort (particularly in the older, frailer cohort of people for whom fludarabine plus cyclophosphamide plus rituximab (FCR) is unsuitable and where background mortality is higher). • The key issue flagged by the EAG is regarding treatment effect varying between populations. • Do you have any additional comments outside of what has been provided for Qs 14?	
Key issue 3: The progression-free utility value applied in the model lacks face validity • Would you expect the progression free quality of life of a person with chronic lymphocytic leukaemia to be higher, lower or the same compared with the age and sex adjusted	Lower. CLL is an incurable disease and does leave patients with significant disease and treatment related morbidities. They will continue to need ongoing follow-up even during stable remission periods

general population of the UK? • Please explain why? *Progression free means the condition has not yet progressed after first-line of treatment	
Key issue 4: Applying the same utility value to the progression free while on second line of treatment (PF 2L) and post-progression survival (PPS) health states may not be reflective of persons' quality of life after progressing on first-line treatment. • Would you expect the quality of life of a person on second line treatment, progression free for chronic lymphocytic leukaemia to be different compared with the quality of life of a person whose condition has progressed after second / later lines of treatment? Please explain why?	Yes. Patients needing second or latter lines of therapy likely have more advanced disease with sorter duration of responses and additional comorbidities (which may be treatment/disease or age-related)
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1) The fixed duration use of the oral I+V has the potential to alter standard of care for CLL patients
2) It has the potential to provide greater benefit for patients with high-risk disease characteristics
3) The slightly higher rate of adverse events are counterbalanced by fixed duration of the treatment compared to current continuous BTKi treatments
4) No problems are foreseen for the use of this combination in specialist haemato-oncology departments and settings
5) The depth and duration of responses with I+V are encouraging but longer follow-up will inform safety and efficacy

Click or tap here to enter text.

Click or tap here to enter text.

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Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Clinical expert statement and technical engagement response form

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Part 1: Treating chronic lymphocytic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Nicolas Martinez-Calle
2. Name of organisation	UK CLL Forum and British Society of Haematology.
3. Job title or position	Consultant Haematologist, Nottingham University Hospitals NHS trust Member of UK CLL Forum executive committee and member of the British Society of Haematology.
4. Are you (please tick all that apply)	✓ An employee or representative of a healthcare professional organisation that represents clinicians? ✓ A specialist in the treatment of people with chronic lymphocytic leukaemia ? ✓ A specialist in the clinical evidence base for chronic lymphocytic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	✓ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to declare

8. What is the main aim of treatment for chronic lymphocytic leukaemia ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Chronic Lymphocytic Leukaemia (CLL) is a chronic and incurable condition. The aim of treatment is obtaining the longest period of progression free survival (PFS) with the best quality of life. This can be achieved with continuous therapy that leads to sustained disease control or with time-limited therapy that achieves deep responses with treatment-free intervals of variable length.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Response in CLL is measured by the internationally standardised IWCLL criteria (International Workshop on Chronic Lymphocytic Leukaemia). It is generally accepted that partial or complete responses are acceptable, provided they are accompanied with resolution of CLL-related symptoms.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic lymphocytic leukaemia?	The treatment of CLL patients who fail all existing and available drug-classes remains the biggest unmet need. Despite the recent approval of novel agents for treatment of CLL, which are now readily available in the treatment pathway, there is still a significant subgroup of patients for whom treatment options are exhausted and who die of progressive CLL. The lack of NICE approved targeted agents for patients in front line who would be otherwise fit for chemoimmunotherapy (CIT) and have non-disrupted TP53 status, is a relevant unmet need for the UK. To date, these patients can only access fixed-duration Venetoclax-Obinutuzumab therapy through the CDF and they have no access to Bruton´s Tyrosine Kinase (BTK) inhibitors through routine commissioning. A novel therapy approach for this subgroup of patients would be highly desirable for both patients and clinicians. Another relevant unmet need is the incorporation of measurable residual disease (MRD) evaluation into the routine clinical practice. It has been now widely demonstrated in large randomised Phase 3 trials that MRD negativity predicts for longer PFS (CLL14, CLL13, GLOW. MURANO, ALLIANCE). MRD could be used as a therapeutic goal, as a tool for tailored therapy and as a tool for disease monitoring/early diagnosis of relapses.

11. How is chronic lymphocytic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The British Society of Haematology (BSH) is the local guideline for treatment if CLL. The UK CLL forum has taken a central role in the development of the updated guidelines, which incorporate acalabrutinib and venetoclax-based regimens, recently appraised by NICE and commissioned by NHSE. The pathway of care is well defined and follows, in England, the algorithms published in the BSH CLL guidelines. There are differences in commissioning in Ireland, Wales and Scotland that may result in variations of this treatment pathway. The current technology (Ibrutinib + Venetoclax) is proposed as an alternative first line treatment for CLL. The potential impact of the technology can be assessed in three different patient populations: 1) Patients with TP53 disruption: In these patients it would constitute an alternative to 12 months of Venetoclax-Obinutuzumab therapy or continuous BTKi. 2) Patients fit for CIT and no TP53 disruption: It would constitute an alternative of the commissioned FCR CIT regimen and the CDF-reimbursed Venetoclax-Obinutuzumab. 3) Patients unfit for CIT and no TP53 disruption: It would constitute an alternative to Venetoclax-Obinutuzimab, BTKi and Obinutuzumab-Chlorambucil. I+V would be a potentially suitable option for all of the above populations based on the efficacy results of the clinical trials presented in the company's submission. For fit patients suitable for FCR I+V would remove the exposure to well know FCR toxicities (significant infection risk/ secondary cancers). In this patient population the greatest benefit, seem to be derived from the unmutated IGHV patient population, with rates of complete response and MRD negativity that are comparable to the whole of FCR-treated population, overcoming the known adverse prognosis of IGVH mutation in the context of chemoimmunotherapy. We believe highlighting this aspect to the committee is relevant, as IGHV mutation

	status could be potentially used as a decision-tool for treatment. However it must be acknowledged that there is no statistical power to draw conclusion on the IGHV mutation subgroups. Further data from the UK FLAIR study will come into play when it becomes available during the next 2-3 years. For patients unfit for CIT, the efficacy demonstrated in the GLOW trial and the health-economic analysis are likely to make this a reasonable treatment alternative in comparison to fixed-duration Venetoclax-Obinutuzumab and continuous BTKi. However, it must be pointed out to the committee that there is some concern from the CLL clinicans with respect to the toxicity of I+V in the elderly patient population, which include a slightly higher than expected sudden/cardiac deaths on the I+V arm of glow. There are some caveats with the interpretation of this deaths which include trial design and geography of the patients enrolled, but it is clear that raises an alarm on the use of Ibrutinib in elderly patients when there are safer alternatives with similar clinical outcomes (albeit more expensive). For the TP53 disrupted population, there is preliminary evidence in the company's submission about the efficacy in this patient group. We highlight this to the committee, as the number of patients with TP53 disruption exposed to I+V is less than 30. In the TP53 disrupted population, continuous therapy seems to be preferred by clinicians given the wider experience on BTK inhibitors in this setting, and it remains to be demonstrated if a fixed duration regimen will remain beneficial with longer follow-up. Although we consider reasonable to assume I+V will lead to good clinical outcomes (based on preliminary data) and acknowledging the unmet need for TP53 disrupted patients is higher, careful consideration needs to be made for I+V in this setting.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I+V is a fixed-duration oral therapy regimen, hence healthcare resource utilisation is likely to be reduced in comparison to the regimens that include intravenous administration of anti-CD20 antibodies. In terms of safety profile there is a group of side effects that are increased in the combination of I+V in comparison to each of these drugs individually, mainly the risk of treatment

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	induced-neutropenia and neutropenic fever and the overall risk of infections. This risks, however, are only temporary, whilst the patient is receiving treatment and on the whole are likely to have a lesser impact on the health-care utilisation as compared to continuous therapy with BTKi and other more toxic fixed-duration regimens such as CIT with FCR or BR. I+V, akin to all the available CLL treatments should be restricted to use under specialised care of a qualified and registered Haematologist or Oncologist. There is no anticipated investment needed for the introduction of the new technology as all the centres will already be familiar with the use of both drugs individually and there are not significant safety concerns of the combination or modifications to treatment delivery derived from their combined use.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	As outlined in the company submission and the EAR report, I+V is likely to be a cost-effective alternative for the treatment of CLL in the first line setting. It is likely to achieve deep and long lasting remissions in the majority of patients, without the need for continuous drug exposure and the side effects associated with it. High rate of undetectable MRD has been reported in both studies, which raises up to 52% for patients on CAPTIVATE and 77% in GLOW, unprecedented figures for first line treatment in CLL. It remains to be demonstrated if the use of Ibrutinib and Venetoclax in combination as opposed to their individual use in succession during the CLL treatment pathway is beneficial. The relative short follow-up of both CAPTIVATE and GLOW studies, which has been highlighted by the EAR report, does not allow for any conclusions to be drawn in this respect. There is a theoretical possibility of retreatment with Venetoclax and/or BTKi at disease relapse, however there is no data regarding the quality of responses of these agents after I+V treatment and whether or not the early use of both agents will compromise the efficacy of the potential second line therapy. Although in theory this could result in a negative impact on PFS and OS for CLL patients, in our opinion, patients exposed to I+V on a fixed duration regimen will be unlikely to develop resistance to these agents. It is biologically plausible to assume the response to

	Ibrutinib and Venetoclax in second line regimens will be comparable to the first line treatment data we have available currently. It is important to highlight that there is a lack of evidence about this at the time of the evaluation of this technology. Experiencing a side-effect and sequelae-free post-treatment period is highly desirable for patients and their clinicians, fully attainable with I+V therapy. This is the aspect that will have the most significant impact in patient´s quality of life, and will make I+V an attractive regimen for the use in the untreated CLL patient population.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? • Would you anticipate ibrutinib plus venetoclax to be more effective in certain populations compared with others? • For example would ibrutinib with venetoclax result in a different risk of disease progression for the FCR-unsuitable compared with FCR suitable population?	The trials have reported early differences in response between IGHV mutated and un-mutated patients, however these subgroup analysis are not statistically powered within the studies to make definitive conclusions about a differential response according to IGHV status. There seems to be a higher rate of response and longer PFS in the un-mutated IGHV patients. Longer follow up of the cohorts might result in the use as IGHV as a predictor of response for I+V regimen. If the observation of the IGHV mutation was demonstrated, IGHV status could be potentially used for treatment decision involving I+V vs Venetoclax-based vs BTKi regimens. However, the evidence is not sufficiently consolidated to consider IGHV as a routine investigation to predict response to I+V and we do not recommend this. There will likely be a higher risk of progression for high-risk CLL patients treated with I+V combination (as compared to standard risk patients), due to the biological particularities of TP53 disruption which result in shorter duration of response with all the currently available CLL therapies. Again, follow-up remains short to conform this hypothesis. As per the FCR suitable and unsuitable CLL patient population, there is no data suggesting differential risk of progression between these two subgroups, provided treatment is delivered with adequate intensity. In the GLOW study, rate

	of discontinuation was 10% as compared to 5% in CAPTIVATE, which might results in shorted PFS due to reduced treatment intensity in the elderly population, however follow-up remain short to conclude about this.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	As mentioned above, all the centres will already be familiar with the use of both drugs individually and there are not significant safety concerns of the combination or modifications to treatment delivery derived from their combined use. The treatment with Venetoclax requires a carefully monitored dose escalation during the first month of treatment, that mitigates the risk of drug-induced tumour lysis syndrome (TLS). The dose escalation recommendations include both inpatient and outpatient monitoring of TLS parameters. Whilst most centres will be familiar with the venetoclax dose escalation schedule, the incorporation of I+V into the available options for front-line therapy will require a revision of each centre's capacity to accommodate a potential increase in number of venetoclax dose escalations.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No other rules will be required to start o stop treatment other than the treatment schedule that was used in the CAPTIVATE and GLOW studies. TP53 status (i.e. 17p deletion and TP53 mutation) might be relevant for the treatment with the I+V combination depending on the final terms of the NICE recommendation.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as	I+V is an entirely oral regimen, although the cost of the drugs are accounted in the economical model, the health-care utilisation during the treatment with intravenous anti-CD20 antibodies is likely to be underestimated in the models and hence, the benefit of I+V underestimated. In addition, the psychological benefit for patients who will be largely free from treatment sequelae (as compared to CIT) and free from ongoing low-intensity

an oral tablet or home treatment) than current standard of care	side effects (as compared to continuous BTKi) is largely unaccounted in the economical models. These improvements constitute an aspect of quality of life that is of high relevance to patients with CLL and their relatives.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Ibrutinib and Venetoclax are both first-in-class targeted agents for the treatment of CLL. Both have significantly changed the landscape of treatment of CLL in both the relapsed and the first line setting, gradually displacing CIT as the preferred treatment option, significantly extending survival and improving quality of life of CLL patients. It is evident from pre-clinical evidence that I+V act synergistically against CLL (Clin Cancer Res. 2015 Aug 15;21(16):3705-15), their combination seems like the logical step-forward in the treatment of CLL aiming at deeper and longer lasting remissions after treatment. The high potency of the combination allows for short and fixed-duration treatment regimen with PFS and time to treatment that may also result in significant cost-savings for the health system. I+V will be specifically addressing the unmet need of novel targeted therapy for younger patients who are fit for CIT, for whom there is no current NICE-recommended alternative apart from CIT regimens such as FCR or BR.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment with I+V implicates undergoing a strict and step-wise dose ramp-up schedule to mitigate the risk of TLS. This carries an impact on patient´s quality of life, particularly related to number of hospital attendances and potential hospital admission for TLS monitoring. It is however no different to what it is already done for treatment with Venetoclax, either alone or in combination with Anti-CD20 antibodies. The main adverse event of the I+V combination from the GLOW and CAPTIVATE clinical trial has been an increase of Haematological toxicity, mainly neutropenia but also thrombocytopenia.

	Grade 3 or more severe neutropenia was reported in 33-35% of patients in the trials, however this did not seem to translate into high rates of neutropenic sepsis. The rates of grade 3 thrombocytopenia reported in GLOW and in CAPTIVATE were 6% and 13%. This potentially increases the risk of transfusion requirements for patients' treatment with I+V compared to each agent alone, although this increase is thought to be relatively small. Other minor AE which might have impact in the patient´s quality of life are Diarrhoea, nausea, arthralgia were present in proportions ranging to 30-65% (all grades) but only 1-3% grade 3 severity. Most of these are therefore mild and not sufficient to modify therapy but undoubtedly affect patient´s life quality.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The use of both agents matches UK practice. Both trials report PFS adequately, albeit CAPTIVATE primary endpoint was response rate rather than PFS. This aspect is less relevant for the analysis and CAPTIVATE data is not randomised. The comparator for GLOW study is O-CLB, which is a regimen that has experienced a significant reduction in use in favour of novel agent combinations such as Venetoclax-Obinutuzumab. Time to next treatment (TTNT) is a relevant outcome in CLL that will be informative for the economic modelling but it has not been reported within the company submission. Assessment of efficacy based on TTNT will complement PFS and constitutes a patient-oriented and clinically relevant endpoint that would be worth considering for this technology.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The FLAIR trial, a UK wide randomised study in front-line CLL in FCR fit population has recently reported preliminary results of the I+V combination, showing an ORR of 88% and 42% of patients achieving MRD negativity after 1 year of treatment. There is still no data available regarding PFS and OS as the follow-up remains relatively short, but the rates of response and MRD are comparable to CAPTIVATE trial. This study will provide randomised evidence in the next 1-2 years to reassess the cost effectiveness of I+V vs FCR with randomised trial data (https://ash.confex.com/ash/2022/webprogram/Paper170463.html)
22. **a) Do you agree with the comparator selection per population below?** **b) Which of the comparators are most relevant per population and why?** **c) Are you aware of any new evidence for the comparator treatment(s) since the publication of the following NICE technology appraisal guidance:** People without a del17p or TP53 mutation FCR suitable: • FCR (TA174) FCR un-suitable: • O-Clb (TA343) • VenO (TA663) • Acalabrutinib (TA689) People with a del17p or TP53 mutation (high-risk) • Acalabrutinib (TA689) • VenO (TA663) • Ibrutinib (TA429)	a) The comparator selection is sound and reflects UK practice. We are in agreement with the comparators that have been excluded by the company, as their clinical use has diminished over the recent years. b) None of the comparators is more relevant than others as in the setting of treatment naive CLL, all options are efficacious and hence, choice of regimen is largely patient-centred. For this reason the approach of the models comparing I+V to all existing regimens is most appropriate in our view. c) To our knowledge there is some new data about the comparators of I+V. The latest updates for the VenO and Acalabrutinib regimens were presented in the 2022 European Haematology Association annual meeting. Five year follow-up data is now available for Acalabrutinib (ELEVATE-TN trial) and for VenO (CLL14 trial). For VenO TTNT data has been published achieving a 5-years rate of 72% alongside 62% of PFS. For Acalabrutinib, 60-month PFS was 71% in the ELEVATE-TN trial.

23. How do data on real-world experience compare with the trial data?	There is no real-world experience data on I+V combination to date that would allow a meaningful comparison with the trial data.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	We foresee no equality issues with this appraisal.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Immaturity of overall survival (OS) and progression free survival (PFS) data • Is there additional longer-term evidence currently available that would reduce the current uncertainty resulting from the immaturity of the data? *Data is immature because of short follow up	There is no additional evidence that would help to reduce the uncertainty of the short follow-up of GLOW and CAPTIVATE studies.
Key issue 2: The approach to generating transition probabilities by extracting age/sex matched general	No additional comments on this aspect.

population mortality from extrapolated PFS, leading to diminishing risks of progression in the surviving cohort (particularly in the older, frailer cohort of people for whom fludarabine plus cyclophosphamide plus rituximab (FCR) is unsuitable and where background mortality is higher). • The key issue flagged by the EAG is regarding treatment effect varying between populations. • Do you have any additional comments outside of what has been provided for Qs 14?	
Key issue 3: The progression-free utility value applied in the model lacks face validity • Would you expect the progression free quality of life of a person with chronic lymphocytic leukaemia to be higher, lower or the same compared with the age and sex adjusted	CLL is a chronic condition and as such we expect the quality of life of a person with CLL after treatment to be slightly reduced to the general population. This reduction is thought to be much smaller than the one expected after chemoimmunotherapy.

general population of the UK? • Please explain why? *Progression free means the condition has not yet progressed after first-line of treatment	
Key issue 4: Applying the same utility value to the progression free while on second line of treatment (PF 2L) and post-progression survival (PPS) health states may not be reflective of persons' quality of life after progressing on first-line treatment. • Would you expect the quality of life of a person on second line treatment, progression free for chronic lymphocytic leukaemia to be different compared with the quality of life of a person whose condition has progressed after second / later lines of treatment? Please explain why?	We would expect to see a deterioration in quality of life on patients who have progressed after second line therapy, in comparison to the quality of life during second line treatment. We agree with this observation of the EAR and we support the attempt to modify this aspect to produce a more realistic economic model for I+V.
Are there any important issues that have been missed in EAR?	None.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. I+V is likely to achieve deep and long lasting remissions in the majority of patients, including those with adverse risk factors such as TP53 mutation, unmutated IGHV and those with other adverse genomic feature. This will be achieved using a 15 month fixed duration regimen and therefore negates the need for indefinite/ continuous drug exposure and the side effects associated with such regimens.

2. It remains to be demonstrated if the use of Ibrutinib and Venetoclax in combination as opposed to their individual use in succession during the CLL treatment pathway is beneficial as compared to other current front line regimens (which in UK practice would mainly represent either V-O or Acalbrutinib monotherapy). The relative short follow-up of both CAPTIVATE and GLOW studies, which has been highlighted by the EAR report, does not allow for any conclusions to be drawn in this respect.

3. The assessment of the I+V technology in the 3 subgroups of patients proposed is sound (TP53 disruption, Fit for CIT and no TP53 disruption, unfit for CIT and no TP53 disruption), we agree with this in full as it will allow consideration of the technology in each of these individual scenarios.

4. We believe the greatest positive impact of the I+V regimen will be on the CIT-fit patients who have no commissioned alternatives for treatment apart from FCR. I+V in the TP53 disrupted population and in the CIT-unfit population is likely to be cost-effective, however, there are caveats to consider in the elderly population (safety) and in the TP53 disrupted (discrete patient numbers and short follow-up), that should be taken into account by the committee.

5. The potential implementation of I+V technology is unlikely to cause significant burden on the health system as both treatments are currently used independently for the treatment of CLL. Indeed health care resources may be lessened by the lack of use of Obinutuzumab in this regimen.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with chronic lymphocytic leukaemia or caring for a patient with chronic lymphocytic leukaemia. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (see section 1.1 and 1.4 to 1.6).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form, please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Thursday 19 January 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with chronic lymphocytic leukaemia or caring for a patient with chronic lymphocytic leukaemia

Table 1 About you, chronic lymphocytic leukaemia, current treatments and equality

1. Your name	Stephen Abrahams
2. Are you (please tick all that apply)	☒ A patient with chronic lymphocytic leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with chronic lymphocytic leukaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	CLL Support (CLLSA)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with chronic lymphocytic leukaemia? **If you are a carer (for someone with chronic lymphocytic leukaemia) please share your experience of caring for them**	I was diagnosed in 2016. Life continued as normal, albeit with active monitoring. I developed Auto Immune Haemolytic Anaemia, which signalled the start of my treatment – Ibrutinib and Venetoclax under the Flair Trial. It took me a while to recover from AIHA, but went back to the gym and running some 6 months later. I remain fit for my age.
7a. What do you think of the current treatments and care available for chronic lymphocytic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	A. The only treatment available on the NHS at the time was FCR (Chemo). There are more options treatments available now, partly I believe due to CV19, thus avoiding numerous hospital visits during that time. For me, I established that FCR (irrespective of its side effects), would have been unlikely to have given me a long period of remission (non mutated) B. I believe that most folk are happy with the choice of treatments available currently. My treatment was over 3 years, some may prefer a shorter period of treatment, although I cannot fault the outcome.
8. If there are disadvantages for patients of current NHS treatments for chronic lymphocytic leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	FCR is still available, the side effects are what one might expect from chemotherapy. This does however suit some. My treatment was 3 years, quite a period to take a powerful drug, others I gather are 12 months. Save for the above, I am not sufficiently familiar with the other current medication available
11. Are there any groups of patients who might benefit more from ibrutinib with venetoclax or any who may benefit less? If so, please describe them and explain why	The Venetoclax in particular works quick swiftly. This may be an advantage both physically and mentally to some patients. Ibrutinib may not suit patients who already have high BP.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	With regards to Venetoclax, this is quite onerous at the beginning, as the dose is very low to start, and is ramped up over time. At the very beginning, this involved 3 or 4 visits to the hospital per week, to monitor for Tumor lysis syndrome. I live close to the hospital, so this monitoring was not too much of an issue for me. I would also say that there was quite a bit of medication to take, other associated drugs too, so one has to be very organised. It was also essential to drink plenty of water whilst undergoing treatment.
12. Are there any potential equality issues that should be taken into account when considering chronic lymphocytic leukaemia and ibrutinib with venetoclax? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I believe that only those with physical difficulties might be disadvantaged, certainly at the beginning. This would depend on their ability to attend their treatment centre regularly at the beginning, and subject to transport, parking etc.. Assistance may be required for patients with sight issues, and/or cognitive impairment.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Immaturity of overall survival (OS) and progression free survival (PFS) data • Is there additional longer-term evidence currently available that would reduce the current uncertainty resulting from the immaturity of the data? *Data is immature because of short follow up	

Key issue 2: The approach to generating transition probabilities by extracting age/sex matched general population mortality from extrapolated PFS, leading to diminishing risks of progression in the surviving cohort (particularly in the older, frailer cohort of people for whom fludarabine plus cyclophosphamide plus rituximab (FCR) is unsuitable and where background mortality is higher). • Would you anticipate the treatment to be more effective in certain populations compared with others? • For example would ibrutinib with venetoclax result in a different risk of disease progression for the FCR-unsuitable compared with FCR suitable population?	
Key issue 3: We consider patient perspectives may	

particularly help to address this issue: **The progression-free utility value applied in the model lacks face validity** • Would you expect the progression free quality of life of a person with chronic lymphocytic leukaemia to be higher, lower or the same compared with the age and sex adjusted general population of the UK? • Please explain why? *Progression free means the condition has not yet progressed after first-line of treatment	
Key issue 4: We consider patient perspectives may particularly help to address this issue: **Applying the same utility value to the progression free while on second line of treatment (PF 2L) and post-progression survival (PPS) health states may not be reflective of**	

persons' quality of life after progressing on first-line treatment. • Would you expect the quality of life of a person on second line treatment, progression free for chronic lymphocytic leukaemia to be different compared with the quality of life of a person whose condition has progressed after second / later lines of treatment? • Please explain why?	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 19 January 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Immaturity of OS and PFS data	Yes/**No**	This issue of immature trial data is not new in the CLL space, as patients can live for a long time with current treatments. If the committee cannot resolve the uncertainties here, they should consider putting ibrutinib with venetoclax in the CDF in order to gather more data, whilst also improving the unmet needs for patients in this indication.
The approach to generating transition probabilities by extracting age/sex matched general population mortality from extrapolated PFS, leading to diminishing risks of progression in the surviving cohort (particularly in the older FCR-unsuitable cohort where background mortality is higher).	Yes/**No**	N/a
The progression-free utility value applied in the model lacks face validity	Yes/**No**	We understand the issue this creates in a potential over-estimation of quality of life for CLL patients who are progression-free as being above that of the general population. However, we wish to emphasise that it is possible for people with CLL to have a quality of life that is very close to the general population.

Applying the same utility value to the PF 2L and PPS health states may not be reflective of patients' quality of life after progressing on first-line treatment	Yes/**No**	We wish to reiterate the point that CLL is generally a well-controlled disease and that people on watch and wait (active monitoring) often have a very good to high quality of life.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma [ID3860]

ERG critique of the company's response to technical engagement

Produced by Aberdeen HTA Group

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Health Economics Research Unit
University of Aberdeen
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Date completed **1 February 2023**

Contains AIC/CIC [Redacted]

Contents

In their response to the technical engagement report, the company addressed each of the issues raised in the EAG report and provided some revised economic analyses. This addendum to the EAG report provides a brief critique of the company response. It should be read in conjunction with the company's technical engagement response document, dated 19 January 2023

The key issues raised in the EAG report are outlined in Table 1. A more detailed summary of each issue can be found in the Executive summary of the main EAG report:

Table 1 Summary of key issues identified by the EAG

ID3860	Summary of issue	Report sections
1.	Immaturity of OS and PFS data	3.2, 3.4, 4.2.6
2.	The approach to generating transition probabilities by extracting age/sex matched general population mortality from extrapolated PFS, leading to diminishing risks of progression in the surviving cohort (particularly in the older FCR-unsuitable cohort where background mortality is higher).	4.2.6
3.	The progression-free utility value applied in the model lacks face validity	4.2.7
4.	Applying the same utility value to the PF 2L and PPS health states may not be reflective of patients' quality of life after progressing on first-line treatment	4.2.7

Company response to the key issues

Issue 1 - Immaturity of OS and PFS data

This issue relates to the EAG concern about the immaturity of progression-free survival (PFS) and overall survival (OS) data with subsequent uncertainty as median survival time was not reached for most of the outcomes (especially for the I+V arm of the trial). The CAPTIVATE and GLOW trials had 38.7 months and 34.1 months follow up respectively. The company argue that median survival times not being reached indicates a lack of events over the time of follow up which could imply that the treatment is efficacious.

The company also presented data including [redacted] of follow up of [redacted] months and 46 months for CAPTIVATE and GLOW trials respectively. The company found that the results obtained on this new updated follow-up were consistent with the previous results submitted, with consistent KM plots for the comparison of the original and updated data cuts.

Non-del17p PFS (INV) rate at [redacted] months using the updated data from CAPTIVATE ([redacted] months) was reported as [redacted] compared with 89.1% at 36 months based on both the 38.7 and [redacted] months data cuts. The hazard ratio ((95%CI); p-value) of IRC-assessed PFS rates of I+V vs O-Clb from original (34.1m) and updated (46m) data cuts in the GLOW trial were 0.22 (0.13, 0.36); p<0.0001 and 0.21 (0.14, 0.33); p<0.0001 respectively.

The EAG acknowledge that the updated data cut show results that are consistent with the original data presented in the company submission. It is somewhat reassuring that the effects relative to other comparators are maintained or slightly improved in the updated indirect treatment comparisons, but these effects remain uncertain. While the consistency of the results from the additional [redacted] of data may help alleviate concerns about uncertainties surrounding the data, the issues around proportionality of hazards over an extended period cannot be addressed by a [redacted] follow up data cut since this assumption is applied for a much longer period.

The EAG notes the company's argument that median survival time not being reached implies that the treatment is efficacious and that the consistency of results of the updated data cut with the original data indicates a consistency in the treatment effect of I+V in the long term. The EAG views this statement as problematic because a lack of events could also be due to the relatively small sample sizes in the analyses and a [redacted] follow up cannot be considered as long-term when comparing first line treatments of CLL.

Issue 2 - generating transition probabilities by extracting age/sex matched general population mortality from extrapolated PFS

This issue relates to the EAGs concern with the company's approach to estimating transition probabilities from PF 1L to PF 2L or PPS by subtracting general population mortality from the extrapolated PFS hazards. This resulted in extrapolation of zero progression risk in the older FCR unsuitable cohort from approximately [redacted] years following treatment initiation with I+V and acalabrutinib – suggesting a cure fraction of [redacted] and [redacted] respectively. In the younger FCR suitable population, with lower background mortality, a risk of progression is maintained much further into the model time horizon. The EAG question the consistency of this, and why the risk of progression, conditioned on survival, should fall lower more quickly in the FCR unsuitable cohort.

The company have responded by noting that the age at which PFS is capped by general population morality is consistent (around 85-86 years) between the populations. This shows that the risk of progression reaches zero in both cohorts around the same age in the model.

However, this happens much later in the time horizon for the younger FCR-suitable cohort [redacted]), when a much smaller proportion remain alive and progression free [redacted]).

The company have further sought clinical opinion that suggests it is plausible that patients still in remission on first line targeted treatment at age 85 are more likely to die than progress. Nevertheless, the company acknowledge that some patients may still progress at that advanced age rather than die. To address this they have also implemented the EAG scenario analysis whereby the transition probability of progression in the FCR unsuitable cohort cannot fall below that of the FCR suitable cohort.

The EAG acknowledge the company's comments that with advancing age patients in remission are more likely to die than progress. However, the EAG does still have concerns that the company's model projects a zero risk of progression for the surviving FCR unsuitable cohort much earlier in the time horizon than it does for the FCR suitable cohort. Whilst we acknowledge methodological limitations in the scenario that ties the progression transition probability in the FCR unsuitable cohort to that in the FCR suitable cohort, the EAG believes it is still useful for exploring this uncertainty.

Issue 3 Progression free utility value

This issues relates to the EAG concern that the progression free utility value derived from GLOW was higher than the age-sex matched value for the UK general population. The EAG believed this may reflect the typically better performance status of patients enrolled in clinical trials and may not be generalisable to typical patients with CLL treated routinely in the NHS. Therefore, the EAG preferred to cap utility at age-sex matched UK general population norms. It may be noted that this change has minimal impact on cost-effectiveness estimates.

The company, in their response to technical engagement have reiterated arguments for why they believe the higher utility value for PFS is plausible, noting consistency with previous CLL trials (CLL14 and ELEVATE-TN) and associated appraisals.[1,2] They have, however, also included scenarios that cap progression free utility at populations norms.

The EAG acknowledge the company's points but suggest that the other trials referred to may also overestimate utility of the typical CLL patient treated in routine NHS practice. It also notes the approach taken in the previous CLL appraisals based on ELEVATE-TN and CLL14,(NICE TA689 and TA663) was to cap utility at general population norms despite the quality of life data collected in the corresponding trials suggesting a higher PF utility value.[1,2] On balance the EAG prefer to retain this approach.

Issue 4 - PF 2L utility

This relates to the EAG's concern that the company apply the same utility value of 0.6 (derived from a previous appraisal) to the progression free second-line (PF 2L) and post-progression survival (PPS) health states. This is despite a large difference in the mortality rate between these states. For the PF 2L state, the EAG preferred to use a utility multiplier based on the progressive disease utility estimate derived from GLOW trial EQ-5D data (= [redacted]) and reserve the lower value of 0.6 for the PPS health state. This is to capture the expected improved quality of life for those responding on second line treatment compared to those who have progressed further and face a higher mortality rate.

In response the company refer to the source from where the value of 0.6 was derived for second line and all other progression states,[3] which they note was applied to the entire progressed disease state in TA669 and TA663 and accepted by the committee.

The EAG note that the source from which the progressive disease value of 0.6 was derived is a relatively old study (2004) which measured quality of life using the EORTC QLQ-C30.[3] A progressed disease value of 0.6 derived from analysis of this older dataset may not be generalisable to a contemporary second line treatment cohort with more targeted treatment options available. The EAG acknowledge that this single value was used and accepted in TA 669 and TA663, both of which used three state models with only one progressed state. A benefit of the company's four state Markov model in the current appraisal is that it provides improved granularity to capture the subsequent treatment pathway and the link between progression and mortality in more detail. In this context, applying the same utility value to the PF 2L and PPS state lacks face validity. Given the above, the EAG still favour the approach of using the multiplier derived from GLOW to assign PF 2L utility and using the value of 0.6 (with age adjustment) for PPS.

Other non-key issues

In addition to addressing the key issues raised in the EAG report, the company have provided some further responses to minor issues raised throughout the EAG report (see company TE response form). Most of these relate to the provision of further scenarios analyses to address uncertainties around extrapolation and other assumptions. Some of the more substantial ones are discussed in the section below under changes to the company's model.

Changes to the company's model

Updates based on new data cuts

As indicated above, and detailed in their technical engagement response, the company have revised their economic model using updated data cuts from the CAPTIVATE and GLOW trials, and updated indirect treatment comparisons.

The parameters in the economic model that are updated as a result of the new data include:

- FCR suitable population
    - The PFS Hazard ratio for I+V versus FCR, which is applied to the FCR reference curve in the base case to derive a PFS curve for I+V. The PFS curves are then used to derive the transition probabilities for PF 1L to PF 2L or PPS.
    - An independently fitted PFS reference curve for I+V which is used in a scenario analysis.
    - The annual pre-proregression mortality rate, which is used to derive the transition probability from PF 1L to death. This has been updated to reflect the 48-month data cut from E1912 trial.[4]
- FCR unsuitable population
    - The PFS reference curves for I+V and O-Clb based on parametric survival analysis of the updated data cut from GLOW.
    - The PFS hazard ratios for I+V versus VenO and I+V versus acalabrutinib, which are applied to the I+V PFS reference curve to derive PFS curves for these respective comparators.
    - The annual pre-proregression mortality rate, which is used to derive the transition probability from PF 1L to death. This has been updated based on the new data cut from GLOW. With the exception of I+V during the first 15 cycles, for which the observed KM data are used, the mortality rate based on the O-Clb arm of GLOW.

Updated hazard ratios for PFS

The EAG accept the company's updates of the PFS hazard ratios from the indirect treatment comparisons based on updated data cuts from the CAPTIVATE and GLOW trials. They provide point estimates that are broadly consistent with the previous estimates but with somewhat tighter confidence intervals. It is reassuring to note that the effect estimates have been maintained with the further follow-up data, and in some cases have shifted more in favour of I+V. For example, against acalabrutinib in the FCR unsuitable population, the point estimate of PFS hazard ratio has shifted more in favour of I+V. Nevertheless, the data do still remain relatively immature in the context of CLL. Whist the fact median PFS has not yet

been reached for I+V in the new data cuts from CAPTIVATE and GLOW is indicative of an efficacious treatment in the FCR and FCR unsuitable populations respectively, there is still uncertainty around the long-term extrapolation of this improved efficacy against the relevant comparators. There are further uncertainties relating to the indirect nature of the comparisons with FCR, VenO, acalabrutinib and ibrutinib.

<u>Extrapolation of the PFS for I+V versus FCR</u>

In line with their original approach, the company use the same Weibull reference curve fitted to digitised long term PFS data for FCR from the E1912 trial.[5] They apply their updated hazard ratio for I+V versus FCR, obtained from their indirect inverse probability for treatment weighting (IPTW) comparison, to this. The update has shifted the hazard ratio slightly more in favour of I+V, from [redacted] to [redacted] and has narrowed the confidence interval. As per the original submission, the company have used the estimated HR when I+V data are weighted to the covariate distribution of the FCR control group (ATC). They appropriately test the HRs based on the ATT and ATO analyses in scenarios.

For the scenario relying on direct extrapolation of I+V PFS data from the CAPTIVATE fixed dose (FD) cohort, the company have refitted and further justified their preferred exponential curve.

For PF 1L to death, the company has re-estimated the annual rate of pre-progression mortality form CAPTIVATE and E1912 and used the E1912 rate capped by general population mortality for both arms as per the original submission. The EAG accepts this approach.

<u>Extrapolation of PFS for I+V, O-Clb, VenO and acalabrutinib</u>

Regarding the parametric curve fitting for I+V and O-Clb based on the updated data cut from GLOW, the EAG is satisfied with the company's process and base case curve selections. The selected exponential curve for I+V minimises the AIC and BIC and provides the second most conservative estimate. The most conservative curve, the generalised gamma, has also been tested by the company in scenario analysis. The revised exponential curve results in a slightly lower projection of PFS for I+V compared to the original submission.

For O-Clb, the revised parametric fitting has resulted in a 5 knot spline model being selected, in place of the previously selected 6-knot spline. With the relatively mature PFS data available for O-Clb, the curve fitting is associated with less uncertainty. The revised curve provides similar, slightly more optimistic projections compared to those in the original

submission. The company have also addressed previous EAG comments on sensitivity analysis around the O-Clb curve, by exploring scenarios that use the more optimistic log-normal and log-logistic curve fits.

The hazard ratio derived from the indirect treatment comparison against VenO remains uncertain and not statistically significant ([redacted]). This is a potentially important point as the cost-effectiveness case against VenO relies on improved efficacy against this fixed dose comparator– leading to QALY gains and downstream cost savings. As the company point out, however, this uncertainty is propagated through probabilistic sensitivity analysis (PSA). It is also worth noting that application of the hazard ratio for VenO to the I+V reference curve appears to underestimate 5-year PFS for VenO as observed in the latest data cut of the CLL14 trial (reported as 62.6% versus [redacted] in the model).[6] This could, however, be due to differences in the populations that have been adjusted for in the anchored MAIC comparison – as the reported 5-year PFS also appears substantially higher for O-Clb in CLL14 compared to that projected in the model from the GLOW trial data (27.0% versus [redacted]).

Against acalabrutinib and ibrutinib, the case for I+V is perhaps more robust due its substantially lower treatment acquisition cost against these treat to progression regimens. The PFS hazard ratio for I+V has improved somewhat with the updated data cut, although confidence intervals remain wide ([redacted]).

Regarding updating of the transition probability from PF 1L to death, the observed Kaplan-Meier data is used for the first 15 cycles for I+V, as per the original submission, to capture early events. For O-Clb and other comparators the company use an annualised pre-progression mortality rate derived from the O-Clb arm of GLOW. The annualised rate is used to derive a constant 28-day transition probability, which is capped by general population mortality. It is also applied to I+V after the first 15 cycles since there were very few death events beyond 15 cycles in the I+V arm from which to derive an ongoing rate. The updated analysis changes the annual rate of pre-progression mortality from [redacted] to [redacted].

Other model updates

The company also note that they have updated the percentage of patients requiring FCR prophylaxis in the FCR suitable population from 0% to 17.6%. They state that this was an error in the original submission. It has a very limited impact on the ICER in the FCR suitable population. *The EAG accept this change*.

The company have also provided a scenario based on comments in the EAG report, to assess the impact of applying once-off third line treatment costs in the model. This has been informed by clinical expert opinion and data from a subgroup of CLL patients in the ibrutinib arm of the RESONATE trial who had received one or two prior lines of treatment at baseline and went on to 3L treatment after progression on ibrutinib.

The EAG is satisfied with the company's work up of the scenario, which helps address the potential impact of this uncertainty. The company found it to have minimal impact on the ICER.

In addition to the changes documented in the TE response, the company appear to have changed elements of the frontline and subsequent treatment cost/utility decrement calculations. This change involves applying these from cycle zero rather than cycle 1 of the model. The EAG picked up on this issue in the EAG report and implemented a fix to the frontline treatment calculations. The EAG did not make the same change to the subsequent line treatment calculations because it conflicted with tunnel state calculations in the model engines which apply a time delay between progression and initiating second line therapy. In their revised model, the company appear to have partially implemented the EAGs correction to the frontline treatment costs (without also adjusting the half cycle correction calculations in the model engines) but they have also altered the subsequent treatment calculations. As a result, the tunnel state (time delay) calculations for initiating subsequent therapy appear to have been corrupted in the model engines.

To address the above issues the EAG has removed these latter undocumented company changes so that the revised company base case reflects only those documented in their response. The EAG has then reimplemented its correction to the frontline treatment calculations in its alternative base case so that these commence from cycle zero. The results of the EAG amended company base case and the EAG alternative base case are provided below. The company may wish to provide an alternative analysis if this is not what they intended.

Revised model output with EAG revisions

Table 2 Company Deterministic Results: FCR-suitable population (EAG amended company base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	12.97	[redacted]						
FCR	[redacted]	10.84	[redacted]	[redacted]	2.13	[redacted]	£6,618	[redacted]	[redacted]

FCR = fludarabine, cyclophosphamide, rituximab; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; WTP = willingness to pay

Table 3 Average results based on the PSA: FCR-suitable population (EAG amended company base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	13.06	[redacted]					
FCR	[redacted]	10.86	[redacted]	[redacted]	2.20	[redacted]	£4,308	[redacted]

FCR = fludarabine, rituximab, cyclophosphamide; ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year

Figure 1 Cost-effectiveness acceptability curve: FCR suitable (EAG amended company base case)

Table 4 Deterministic Results: FCR-unsuitable population (EAG amended company base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.52	[redacted]						
O-Clb	[redacted]	7.94	[redacted]	[redacted]	1.58	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.24	[redacted]	[redacted]	0.28	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	9.66	[redacted]	[redacted]	-0.14	[redacted]	Dominant	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; O-Clb = obinutuzumab + chlorambucil; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay
†Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Table 5 Average results based on the PSA: FCR-unsuitable population (EAG amended company base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	9.52	[redacted]					
O-Clb	[redacted]	7.94	[redacted]	[redacted]	1.58	[redacted]	Dominant	[redacted]
VenO	[redacted]	9.35	[redacted]	[redacted]	0.17	[redacted]	Dominant	[redacted]
Acalabrutinib	[redacted]	9.71	[redacted]	[redacted]	-0.19	[redacted]	less costly, less effective (£4,781,507)	[redacted]

ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab
†Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Figure 2 Cost-effectiveness acceptability curve: FCR unsuitable (EAG amended company base case)

Table 6 Deterministic Results: High-risk population (EAG amended company base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.52	[redacted]						
Ibrutinib	[redacted]	9.66	[redacted]	[redacted]	-0.14	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.24	[redacted]	[redacted]	0.28	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	9.66	[redacted]	[redacted]	-0.14	[redacted]	Dominant	[redacted]	[redacted]

ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + obinutuzumab; WTP = willingness to pay

Table 7 Average results based on the PSA: High-risk population (EAG amended company base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	9.52	[redacted]					
Ibrutinib	[redacted]	9.69	[redacted]	[redacted]	-0.18	[redacted]	less costly, less effective (£2,929,763)	[redacted]
VenO	[redacted]	9.32	[redacted]	[redacted]	0.20	[redacted]	Dominant	[redacted]
Acalabrutinib	[redacted]	9.69	[redacted]	[redacted]	-0.17	[redacted]	less costly, less effective (£7,236,246)	[redacted]

ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; VenO = venetoclax + Obinutuzumab; †Represents ICER/QALY forgone as it is in the south-west quadrant (less costly; less effective)

Figure 3 Cost-effectiveness acceptability curve: High-risk (EAG amended company base case)

EAG base case with update model inputs

Table 8 Deterministic Results: FCR-suitable population (EAG alternative base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	12.97	[redacted]						
FCR	[redacted]	10.84	[redacted]	[redacted]	2.13	[redacted]	£9,137	[redacted]	[redacted]

FCR = fludarabine, cyclophosphamide, rituximab; ICER = incremental cost-effectiveness ratio; INMB = incremental net monetary benefit; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year; WTP = willingness to pay

Table 9 Average results based on the PSA: FCR-suitable population (EAG alternative base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	13.10	[redacted]					
FCR	[redacted]	10.84	[redacted]	[redacted]	2.25	[redacted]	£5,578	[redacted]

FCR = fludarabine, rituximab, cyclophosphamide; ICER = incremental cost-effectiveness ratio; I+V = ibrutinib + venetoclax; LY = life year; QALY = quality-adjusted life year

Figure 4 CEAC for EAG alternative base case: FCR-suitable (EAG alternative base case)

Table 10 Deterministic results: FCR unsuitable (EAG alternative base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.52	[redacted]						
O-Clb	[redacted]	7.94	[redacted]	[redacted]	1.58	[redacted]	Dominant	[redacted]	[redacted]
VenO	[redacted]	9.24	[redacted]	[redacted]	0.28	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	9.66	[redacted]	[redacted]	-0.14	[redacted]	less costly, less effective (£4,106,479)	[redacted]	[redacted]

Table 11 Average results based on the PSA: FCR unsuitable (EAG alternative base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	9.52	[redacted]					
O-Clb	[redacted]	7.94	[redacted]	[redacted]	1.57	[redacted]	Dominant	[redacted]
VenO	[redacted]	9.33	[redacted]	[redacted]	0.19	[redacted]	Dominant	[redacted]
Acalabrutinib	[redacted]	9.70	[redacted]	[redacted]	-0.18	[redacted]	less costly, less effective (£2,978,237)	[redacted]

Figure 5 CEAC for EAG alternative base case: FCR unsuitable (EAG alternative base case)

Table 12 Deterministic results: High-risk (EAG alternative base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £20,000)	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs			
I+V	[redacted]	9.52	[redacted]						
Ibrutinib	[redacted]	9.66	[redacted]	[redacted]	-0.14	[redacted]	less costly, less effective (£1,881,801)	[redacted]	[redacted]
VenO	[redacted]	9.24	[redacted]	[redacted]	0.28	[redacted]	Dominant	[redacted]	[redacted]
Acalabrutinib	[redacted]	9.66	[redacted]	[redacted]	-0.14	[redacted]	less costly, less effective (£4,106,479)	[redacted]	[redacted]

Table 13 Average results based on the PSA: High-risk (EAG alternative base case)

Technologies	Total			Incremental			ICER	INMB (WTP = £30,000)
	Costs	LYs	QALYs	Costs	LYs	QALYs		
I+V	[redacted]	9.52	[redacted]					
Ibrutinib	[redacted]	9.69	[redacted]	[redacted]	-0.17	[redacted]	less costly, less effective (£1,494,544)	[redacted]
VenO	[redacted]	9.33	[redacted]	[redacted]	0.19	[redacted]	Dominant	[redacted]
Acalabrutinib	[redacted]	9.70	[redacted]	[redacted]	-0.18	[redacted]	less costly, less effective (£2,883,732)	[redacted]

Figure 6 CEAC for EAG alternative base case: High-risk (EAG alternative base case)

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