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

Part 1
For Onscreen – Contains **redacted** information

Technology appraisal rare disease committee assessing ID6232 as a single technology appraisal [ACM1, 19 February 2026]

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Company: AstraZeneca

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on chronic lymphocytic leukaemia

CLL is a malignant disorder of the white blood cells (lymphocytes)

Causes

- Gene controlling blood development ➔ bone marrow produces too many $CD5^+$ B lymphocytes ➔ do not work properly.

Epidemiology

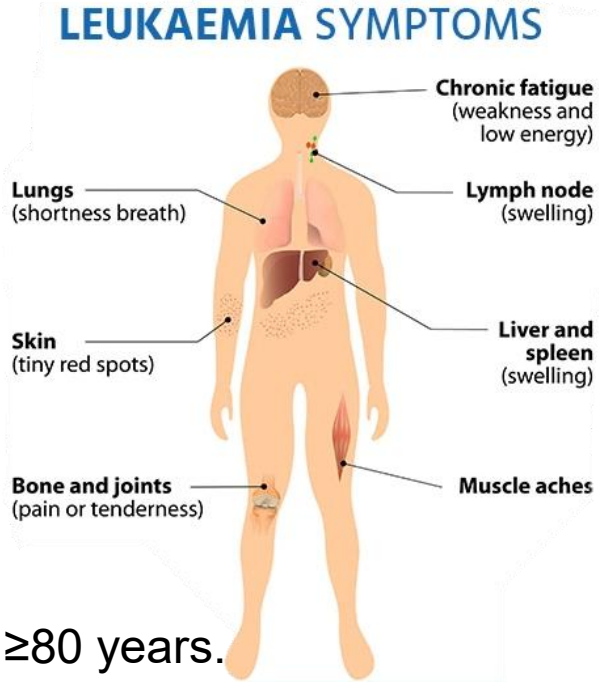
- CLL most common type of leukaemia with approximately 4,000 people diagnosed each year in UK.
- Risk of developing CLL increases with age and is more common in men (approximately 63% are men).

Diagnosis and classification

- Physical examination and complete blood counts determine the clinical staging.
- 'High-risk' disease is defined by the presence of del(17p) or TP53 mutation.

Symptoms and prognosis

- CLL usually progresses slowly, and symptoms develop over time.
- Considerable burden of symptoms and recurrent infections impact quality of life.
- High-risk predicts aggressive disease course & poor prognosis.
- 5-year survival rate is about 95% for those <60 years, and around 70% for those aged ≥80 years.



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Abbreviations: $CD5^+$, cluster of differentiation 5+; CLL, Chronic lymphocytic leukaemia; del, deletion; TP53, tumour protein p53.

Patient perspectives

CLL impacts physical, mental, social, and financial well-being

Joint submissions from a patient expert, Leukaemia Care, Blood Cancer UK, Leukaemia UK, CLL Support and Lymphoma Action

The condition

- Living with CLL can have emotional and psychological impact on patients and families.
  - CLL creates a "ripple effect" impacting on the whole family.
  - Caring for someone with CLL can place significant, sometimes exhausting, demands on family members and carers.
  - CLL patients may feel generally well but still report moments when they need to depend on family for support unexpectedly.
  - Initial diagnosis often brings emotional distress, including fear and uncertainty.

"A patient's treatment preference is shaped by their individual health and social circumstances, including their ability to follow treatment schedules, continue normal work and family activities."

"Patients prioritise treatments that improve survival but also strongly value quality of life and manageable side effects."

What is important to patients and unmet need

- Patients value effective treatments but also prefer options with fewer side effects.
- Since CLL is a long-term illness with multiple lines of therapy, having a range of treatment options is important to support QoL at diagnosis and at relapse.
- Having AV would give patients and clinicians greater flexibility to choose the option that best fits each individual.

Abbreviations: CLL, chronic lymphocytic leukaemia; QoL, quality of life.

Clinical perspectives

Potential to provide additional fixed-regimen treatment option

Submissions from a clinical expert, UK CLL Forum and British Society of Haematology

- Current treatment landscape:
  - Induce remission by clearing disease in bone marrow and nodes and maximising PFS with best possible QoL.
  - Treatment options are categorised into fixed-duration venetoclax regimens and continuous BTKi therapies and expected duration of treatment is a key consideration for patients.
- Unmet need:
  - CLL affects all ages but is most common in older adults, with a typical diagnosis age of about 70.
  - Patients with high-risk genetic features (such as TP53 aberrations or unmutated IgHV).
  - For CLL patients who have exhausted all available drug classes.
- Potential benefits of AV:
  - AV is an all-oral, fixed-duration regimen with a favourable toxicity profile that does not require patients to travel and attend hospital for treatment, unlike VenO which has an IV element.
  - Fixed-duration regimens offer time off treatment and reduce the risk of long-term toxicity and development of additional co-morbidities.

Abbreviations: AV, acalabrutinib with venetoclax; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; IgHV, Immunoglobulin heavy-chain variable region; IV, intravenous; PFS, progression free survival; QoL, quality of life; TP53, tumour protein p53; VenO, venetoclax with obinutuzumab.

Equality considerations

- Company and EAG did not identify any equality issues.
- Clinical expert submission:
    - Differences in NHS infrastructure between tertiary care centres and district general hospitals may cause inequality because smaller hospitals may not have the monitoring capacity or bed availability required.
    - Obinutuzumab infusions require inpatient day-unit capacity for TLS monitoring, which is not consistently available across trusts, unlike outpatient BTKi therapy.
- Patient expert submission:
    - Financial barriers such as travel, parking, lost income, childcare, and limited digital access affect treatment.

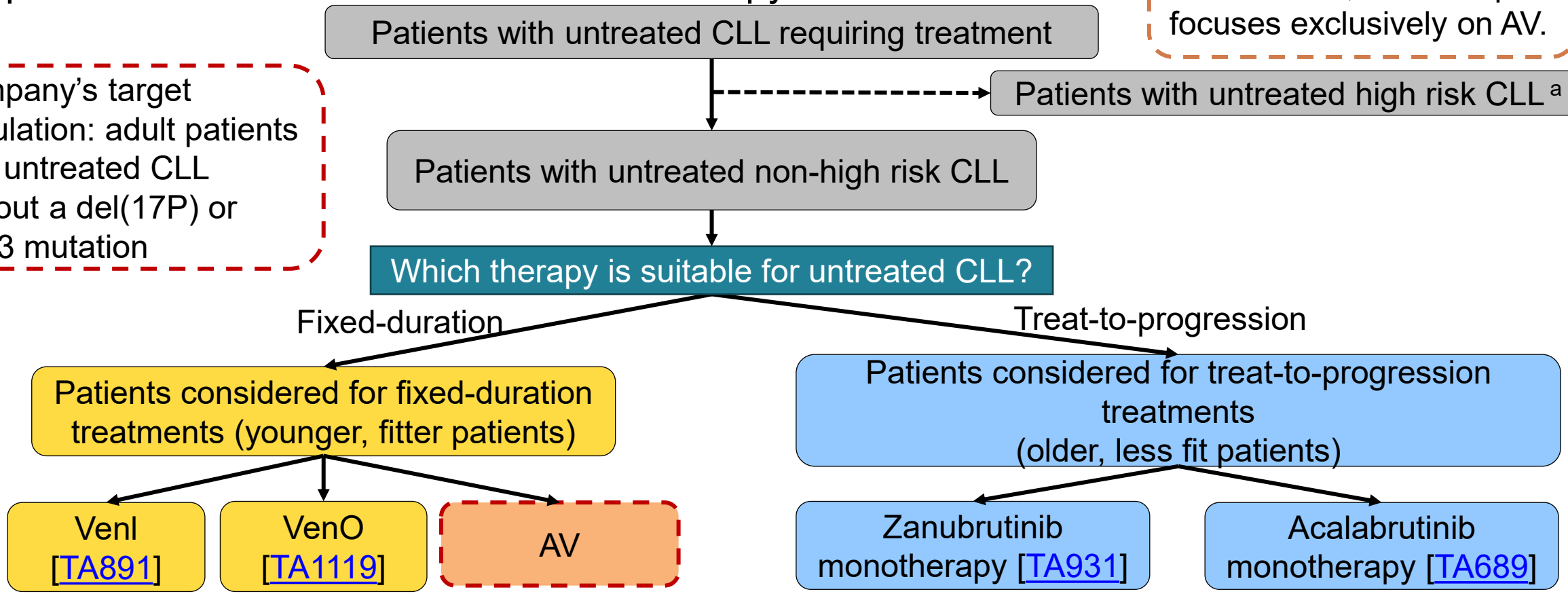
Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; TLS, tumour lysis syndrome.

Company's proposed positioning for AV

AV positioned as first-line fixed-duration therapy

Note: Company did not include AVO, so this topic focuses exclusively on AV.

Company's target population: adult patients with untreated CLL without a del(17P) or TP53 mutation



- Treatment selection is guided by age, IgHV status, comorbidities (using CIRS and ECOG PS scores), concomitant medications, and individual patient preferences.
- AstraZeneca not submitting for reimbursement in high-risk population (mutated TP53 or del[13p]), therefore treatment pathway for high-risk CLL not included in figure.

- In clinical practice, how is fitness determined?
- which patients receive FD therapies, and which patients receive TTP therapies?

Abbreviations: AV, acalabrutinib with venetoclax; AVO, acalabrutinib with venetoclax and obinutuzumab; CIRS, cumulative illness rating scale; CLL, chronic lymphocytic leukaemia; ECOG, Eastern cooperative oncology group; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Technology (Acalabrutinib [Calquence] with venetoclax [Venclyxto], AstraZeneca)

Marketing authorisation	• Acalabrutinib in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. • Approved by MHRA in August 2025.
Mechanism of action	• AV: act through complementary mechanisms, acalabrutinib inhibits BTK-driven CLL proliferation and venetoclax induces BCL-2-mediated cell death.
Administration	• Acalabrutinib: oral tablet (100mg) taken twice daily from Day 1 of Cycle 1 until Day 29 of Cycle 14. 28-day treatment cycles for 14 cycles. • Venetoclax: oral tablet taken once daily starting from Day 1 of Cycle 3 with gradual weekly dose increases over 5 weeks: 20mg, 50 mg, 100 mg, 200 mg and 400 mg by Day 1 of Cycle 4. Venetoclax continued at 400mg once daily until Day 28 of Cycle 14. 28-day treatment cycles for 12 cycles.

Price	• The list price of acalabrutinib (company has a simple PAS approved):
	  ○ 60-tablet pack (100 mg): £5,059.00
	• The list price of venetoclax (PAS approved, unknown to AZ):
	  ○ 14-tablet pack (10 mg): £59.87
	  ○ 7-tablet pack (50 mg): £149.67
	  ○ 7-tablet pack (100 mg): £299.34 (larger pack sizes have same cost per tablet/mg).

EAG

- MA for AV applies independent of mutation status; company's modelling limited to non-mutated population only (Key issue 7).

Abbreviations: AV, acalabrutinib with venetoclax; AZ. AstraZeneca; BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; MA, marketing authorisation; MHRA, medicines and healthcare products regulatory agency; PAS, patient access scheme.

Key issues

*Under the equivalence assumption, ICERs are most sensitive to cost changes

N	Issue	ICER impact*
1	Lack of comparison to acalabrutinib and zanubrutinib treat-to-progression monotherapies	Unknown
2	Generalisability of AMPLIFY trial age and fitness to target NHS population	Small
3	Reliance on assumption of equal efficacy for AV, VenI and VenO	Unknown
4	Modelling of time-on-treatment and relative dose intensity for AV, VenI and VenO	Moderate
5	Choice of health state utility values used in the model	Small
6	Proportion and distribution of subsequent treatments	Moderate

Other issues

N	Issue	ICER impact
7	Extending consideration to people with untreated CLL with 17p deletion or TP53 mutation	Small

 Abbreviations: AV, acalabrutinib with venetoclax; CLL, chronic lymphocytic leukaemia; TP53, tumour protein p53; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Key issue 1: Lack of comparison to acalabrutinib and zanubrutinib treat-to-progression monotherapies

Unknown ICER impact

Company: VenI and VenO are only relevant comparators; EAG: acalabrutinib and zanubrutinib monotherapies are also relevant comparators

Background

- NICE scope included acalabrutinib (TA689) and zanubrutinib (TA931) (TTP comparators), for people without a 17p deletion or TP53 mutation for whom FCR or BR is unsuitable.

Company

- VenI and VenO (dual therapies currently approved for untreated CLL) only relevant comparators to AV (fixed-duration therapy).
- In non-high risk CLL: FD regimens used for younger, fitter patients, whereas TTP therapies used in older, less-fit.
- UK clinical experts: AV not expected to impact treatment decisions for those better suited to TTP therapies.
- TA931 zanubrutinib: Committee accepted that a new therapy does not change decision to use FD or TTP.

EAG comments

- FD and TTP regimens differ, but both are appropriate first-line options in non-high-risk CLL.
- In NHS practice, clinicians choose treatments based on judgement and patient preference, not rigid age/fitness rules → excluding TTP therapies risks overlooking real-world practice.
- EAG experts: AV could expand dual-therapy use beyond VenO/VenI due to more tolerable safety profile of AV.
- TTP monotherapies more likely to be used where hospitals lack the infrastructure for dual-therapy regimens.

Should acalabrutinib and zanubrutinib (treat-to-progression monotherapies) be considered as comparators for acalabrutinib plus venetoclax (fixed-duration)?

Abbreviations: AV, acalabrutinib with venetoclax; BR, bendamustine with rituximab; CLL, chronic lymphocytic leukaemia; FD, fixed duration; FCR, fludarabine with cyclophosphamide and rituximab; TA, technology appraisal; TTP, time-to-progression; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

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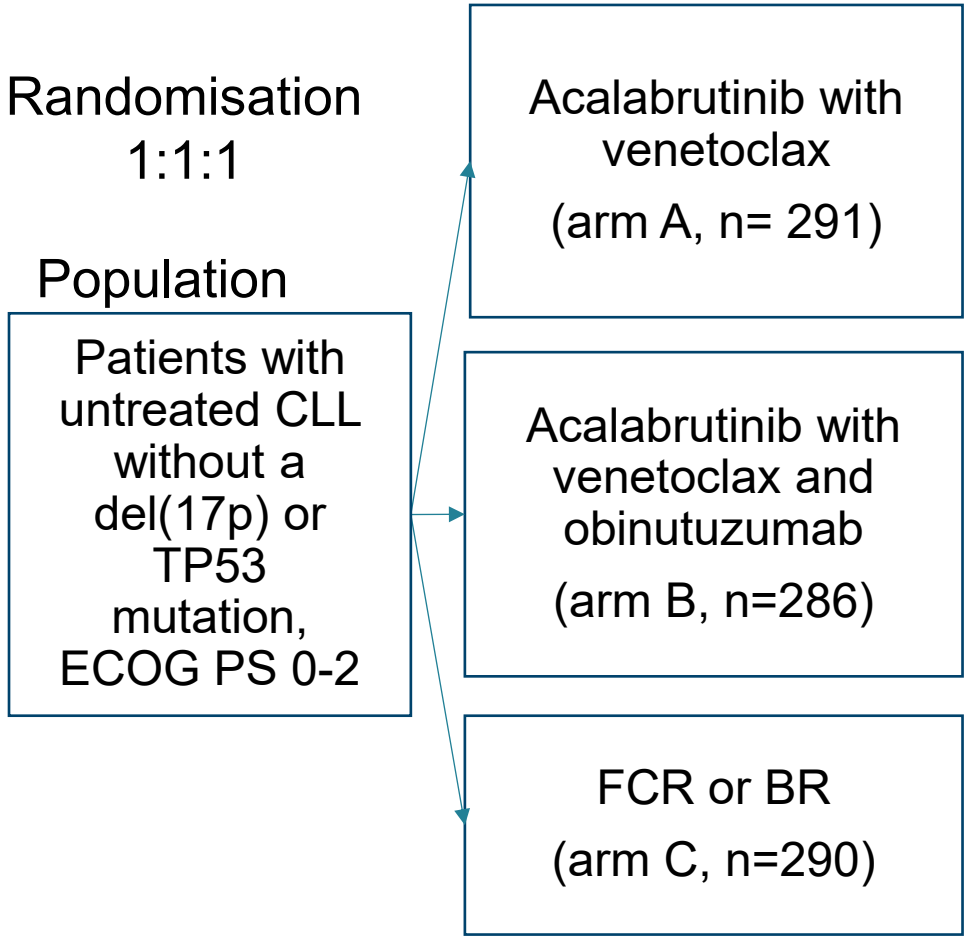
Key clinical trial: AMPLIFY*



	AMPLIFY
Design	Ongoing phase 3, open label, randomised, multicentre
Population	Adult patients with untreated CLL who had an ECOG PS score of 0 to 2 and without a del(17p) or TP53 mutation
Key inclusion criteria	Eligible for chemo
Intervention	AV or AVO
Comparator(s)	Investigator's choice (FCR or BR)
Primary outcome	IRC-assessed PFS
Key secondary outcomes	MRD negativity rate, OS, HRQoL, EFS, Investigator-assessed PFS, AEs
Locations	27 countries (including the UK)
Used in model?	Yes

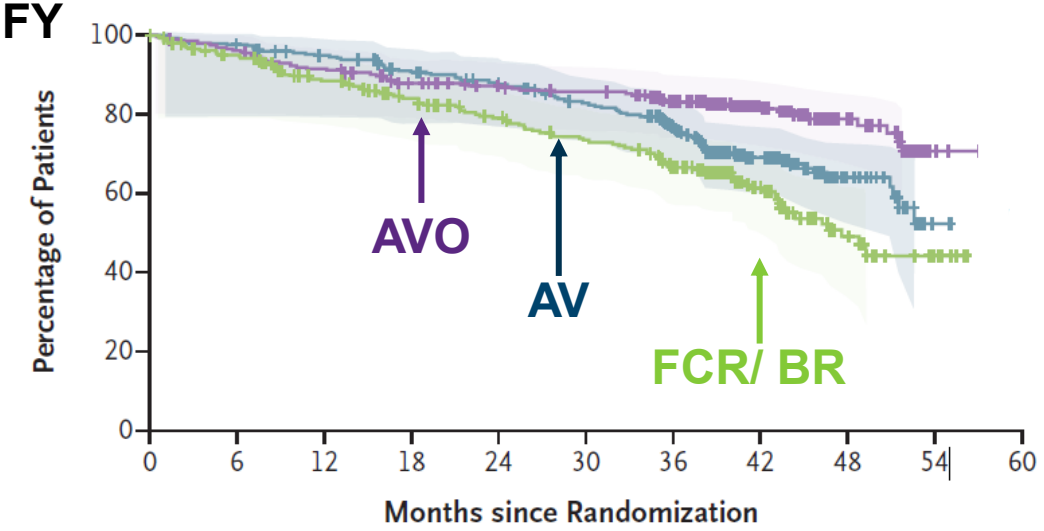
*See appendix for trial dosing regimen.

Is the trial population generalisable to all patients without high-risk mutations?

Abbreviations: AE, adverse event; AV: acalabrutinib with venetoclax; AVO, acalabrutinib with venetoclax and obinutuzumab; BR, bendamustine with rituximab; CLL, chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance-status; EFS, event free survival; FCR, fludarabine with cyclophosphamide and rituximab; HRQoL, health-related quality-of-life; IRC, independent review committee; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; TP53, tumour protein p53.

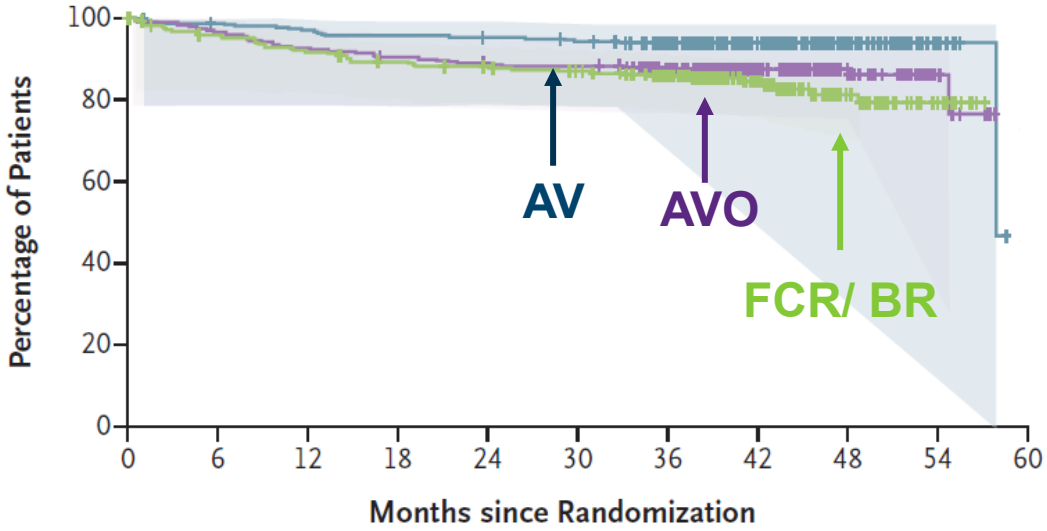
Key clinical trial results – AMPLIFY (PFS and OS, data cut 30th April 2024), median follow up 40.8 months

Figure: IRC-assessed PFS Kaplan-Meier plot for AMPLIFY



No. at Risk											
AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR or BR	290	236	208	189	170	154	127	66	28	6	0

Figure: OS Kaplan-Meier plot for AMPLIFY (FAS)



No. at Risk											
AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10	0
FCR or BR	290	247	236	228	223	217	182	98	45	13	0

Kaplan-Meier estimates of PFS probability by timepoint (%)

	Months	AV arm % (95% CI)	FCR/ BR arm % (95% CI)
PFS	24	[redacted]	[redacted]
	36	76.5 [redacted]	66.5 [redacted]
OS	36	94.1% [redacted]	85.9% [redacted]

PFS and OS hazard ratios

	HR (95% CI; P-value)
PFS	0.65 (0.49, 0.87; P= 0.004)
OS	0.33 (0.18, 0.56; P <0.001)

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Abbreviations: AV, acalabrutinib with venetoclax; AVO, acalabrutinib with venetoclax and obinutuzumab; BR, bendamustine with rituximab; CI, confidence interval; FAS, full analysis set; FCR: fludarabine with cyclophosphamide and rituximab; HR, hazard ratio; IRC, independent review committee; OS, overall survival; PFS, progression-free survival.

Small ICER impact

Key issue 2: Generalisability of AMPLIFY trial age and fitness to target NHS population (1)

Company: mean trial age is 59.9 years; EAG: AMPLIFY trial age is too young vs clinical practice.

Background

- Trial population is younger than expected population in NHS practice; EAG state: around 70 years.

Company

- Model starting age: 59.9 years (= mean baseline age in AMPLIFY, where only [redacted] on AV >75 years).
- Conducted subgroup analysis by age → results favoured AV for both PFS and OS.
- Company UK experts: 59.9 years is representative of patients expected to receive AV or other FD therapies in UK clinical practice.
  - Untreated non-high risk CLL generally younger and fitter than both the overall UK CLL population and subgroup of patients more suitable for TTP therapies. Confirmed by experts in TA931 (zanubrutinib) and shown in CORE study (multicentre, observational cohort study of existing data from clinical practice).
- Differentiation by suitability for FD vs TTP therapies only recently been adopted in UK clinical practice
- TA891 VenI: starting age of 58 years was assumed for FCR/BR-eligible population (CAPTIVATE FD), reflecting typically fitter patients most comparable to those eligible for AV→ consistent with the company base case age.

Abbreviations: AV: acalabrutinib with venetoclax; BR, bendamustine with rituximab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine with cyclophosphamide and rituximab; FD, fixed duration; OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTP, time-to-progression; VenI, venetoclax with ibrutinib.

Key issue 2: Generalisability of AMPLIFY trial age and fitness to target NHS population (2)*

Small ICER impact

EAG comments

- Concerns about generalisability of trial findings and treatment benefits to older CLL patients.
- EAG experts and BSH 2025: age- or fitness-based grouping does not reflect NHS practice.
- EAG clinical experts: mean age for treatment of CLL in the UK is around 70 years.
- UK-RWE: median age of 71.3 years at diagnosis.
- Company subgroup analysis used small sample size. Few events in patients > 65 years → results are underpowered and should be interpreted with caution.
- AV's licence not fitness-based but AMPLIFY aligns with FCR/BR-eligible cohorts → loosely aligning with current fitness-guided first-line choices for dual or mono first line therapy.
- Amended model starting age to 71 years (TA891 VenI; used GLOW [mean age 71] for FCR-unsuitable/ high-risk patients and CAPTIVATE FD [mean age 58] for FCR-suitable patients).
- Scenario analysis: use company's preferred starting age of 59.9 years, based on the AMPLIFY trial mean.
- No meaningful variation in treatment outcomes observed between younger and older patients.

SACT data for untreated CLL cohort in NHS

- Mean starting age 64-65 for VenO, 62-66 for VenI (*see appendix for overview and critique).

Clinical expert

- AMPLIFY population is broadly representative of real-world CLL in age, risk features, and comorbidities.

Are the trial findings generalisable to those who would be offered AV?

Abbreviations: AV: acalabrutinib with venetoclax; BR, bendamustine with rituximab; BSH, British Society for Haematology; CLL, chronic lymphocytic leukaemia; FCR, fludarabine with cyclophosphamide and rituximab; FD, fixed duration; RWE- real-world evidence; TA, technology appraisal; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Summary of key trials used in ITC

	CAPTIVATE FD	GLOW	CLL13	CLL14
Study Design	Open-label, phase 2 single-arm trial.	RCT, phase III, open-label.	RCT, phase III, open-label.	RCT, phase III, open-label.
Population	Previously untreated CLL/SLL, age ≤70, ECOG 0–2.	Previously untreated CLL, age ≥65 or age 18–64, ECOG ≤2.	Fit, untreated CLL without TP53 aberrations.	Previously untreated CLL with comorbidities.
Intervention of interest (N)	VenI (159)	VenI (106)	VenO (229)	VenO (216)
Comparator	Placebo	Chlorambucil + obinutuzumab	Chemoimmunotherapy (FCR or BR)	Chlorambucil + obinutuzumab
NICE evaluation	TA891	TA891	TA1119	TA1119, TA891

Abbreviations: BR: bendamustine with rituximab; CLL, chronic lymphocytic leukaemia; ECOG , Eastern Cooperative Oncology Group; FCR: fludarabine with cyclophosphamide and rituximab; SLL, small lymphocytic leukaemia; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Establishing relative efficacy vs VenO and VenI*

Company: STC vs VenI, VenO and Bucher ITC vs VenO. EAG: analyses biased in favour of AV

Unanchored Simulated Treatment Comparison

- Primary analyses to compare AV vs VenI and VenO. Used trials: AMPLIFY (AV), GLOW and CAPTIVATE FD (VenI), and CLL14 (VenO). *See appendix for trial details.
- Estimated differences in mean PFS and OS (RMST) rather than HRs due to PH assumption being violated.

EAG

- PH is subjective, HRs beneficial in decision-making. PH assessment not a factor in unanchored comparisons.
- Unanchored STC is least robust form of ITC and relied on assumption of all relevant TEMs being observed.
  - NICE TSD 18 notes the assumption is rarely met, especially in oncology due to unmeasured confounding.
- All trials included TP53/del(17p) mutation which could not be adjusted for as subgroup was not included in AMPLIFY- results biased towards AV when AV is likely inferior.
- Concerns with pooling GLOW and CAPTIVATE for VenI comparison.

Anchored Bucher ITC

- Company compared AV vs VenO using AMPLIFY and CLL13 (FCR/BR as common comparator).

EAG

- Imbalances between AMPLIFY and CLL13 likely overestimate AV benefit:
  - proportion of people with ECOG = 0, [redacted]% in AV (AMPLIFY) vs 72.1% in VenO (CLL13).
  - higher FCR usage in CLL13 suggests fitter population supported by longer PFS in CLL13 than AMPLIFY.

Abbreviations: AV, acalabrutinib with venetoclax; ECOG, Eastern Cooperative Oncology Group; ITC, indirect treatment comparison; HR, hazard ratios; PH, proportional hazards; RMST, restricted mean survival time; STC, simulated treatment comparison; TEMs, treatment effect modifiers; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

ITC approaches and feasibility*

Uknown ICER impact

Company- ITC feasibility

	Feasible (EAG's view)	Undertaken (by company)	Company justification/ results
Bucher ITC **Unanchored STC**	Yes	Yes	*See results in appendix
NMA	Yes	*No*	Heterogeneity and TEMs distributions violates assumptions
Unanchored MAIC	Yes	*No*	Poor covariate overlap across relevant studies reduces ESS
ML-NMR	Yes	*No*	Lack of IPD, inconsistent covariates and uncertain TEM validity

EAG comments

- Prefers NMA, MAIC or ML-NMR; IPD available for AMPLIFY. Reliance on unanchored STCs poorly justified.
- NMA: Heterogeneity does not preclude NMA, and results may still inform decisions. Company could have tested excluding studies violating assumptions at clarification but declined.
- MAIC: Still feasible while not all TEMs consistently reported across trials, company did not provide ESS estimates. Company used STC, which assumes overlapping covariates across trials → potential source of bias.
- ML-NMR: optimal ITC with only limitation being covariate reporting across studies which also applied to STC.
- Requested Bucher ITC for AV vs VenO in populations aged ≥ 65 years of AMPLIFY and CLL13 at clarification. Company declined explaining small sample size.

What is the committee's view of the company's ITCs? What ITC methodology is the most appropriate?

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Abbreviations: AV, acalabrutinib with venetoclax; ESS, effective sample size; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NMA, Network meta-analysis; PH, proportional hazards; STC, simulated treatment comparison; TEMs, treatment effect modifiers; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Key issue 3: Reliance on assumption of equal efficacy for AV, VenI and VenO

Uknown ICER impact

Company assumes AV efficacy = VenI and VenO across PFS, TTP, and PPS.

Company

- Suggests ITC results and Delphi panel support equivalence.
- Delphi panel results:
  - 33/93 (35%) invited experts participated, with 67% and 48% response rates in round 1 and 2, respectively.
  - Consensus reached: AV considered suitable alternative to VenI and VenO for PFS, OS, resource use with more favourable safety profile than VenI and comparable to VenO. Similar HRQoL between AV and VenI.
  - No consensus on whether equivalent TTNT (insufficient data) and equal HRQoL for AV vs VenO.

EAG comments

- EAG clinical experts: question validity of AV = VenI and VenO efficacy assumption. Consider VenI efficacy > AV.
- AV has improved cardiovascular safety compared to VenI but easily managed in NHS→ limited advantage.
- AMPLIFY: young/ fit population; lower 36m PFS vs VenI (AV 76.5% vs VenI 88%), likely due to pharmacodynamic distinction between ibrutinib and acalabrutinib. Less AF with AV.
- Unanchored MAIC (Munir et al. 2025) suggests PFS and uMRD superiority of VenI (pooled CAPTIVATE FD and GLOW) over AV: VenI vs AV PFS HR = 0.53 (95% CI: 0.33–0.85; p=0.0085).
- Maintain equivalence in base case. Relax assumption in PSA to capture efficacy differences.
- Explores scenario modelling inferior efficacy outcomes for AV → ICER increases across all scenarios.

Is it reasonable to assume equal efficacy between VenI, VenO and AV?

Abbreviations: AV, acalabrutinib with venetoclax; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; HRQoL: health-related quality-of-life IPD, individual patient data; ITC, indirect treatment comparison; MAIC, Matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NMA, Network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; PPS, post-progression survival; STC, simulated treatment comparison; TEMs, treatment effect modifiers; TTP, time-to-progression; uMRD, undetectable minimal residual disease; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

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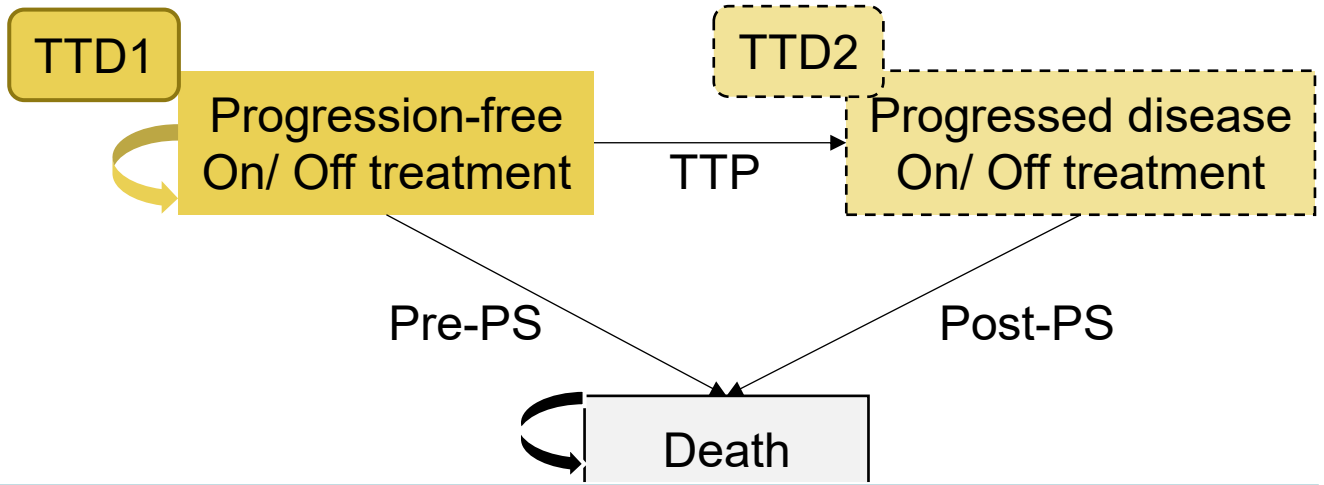
Company's model overview

- Semi-Markov state-transition cohort model, lifetime time horizon of 40 years, 28-day cycle.
- Company used semi-Markov model rather than PSM due to immature OS data from AMPLIFY.
- 3 mutually exclusive health states:
  1. progression free (PF),
  2. progressed disease (PD),
  3. and death.
  - Additional 'on' and 'off' treatment sub-states within PF and PD.

- AMPLIFY: PF → PD & PF → death.
  ASCEND: PD → death.
- All patients enter model in PF on-treatment state and transition between states according to disease progression or death.



Technology affects:	
Costs by having different	• Mode of administration and ToT to comparators. • AE profile to comparators; Acquisition cost to comparators. • % having subsequent therapy and types of treatments.
QALYs by	• Having a different ToT to comparators. • Having a different AE profile to comparators.

Impact on ICER
• Assumption of equal efficacy across treatments; unknown but any deviation potentially moderate to large impact
• Modelling of ToT or completion rate for each treatment; large
• Modelling of subsequent treatments; large

Abbreviations: AE, adverse event; Post-PS: post-progression survival; Pre-PS: pre-progression survival; PSM, partitioned survival model; TTD: time to treatment discontinuation; ToT, time on treatment; TTP: time to progression.

Key issue 4: Modelling of ToT and RDI for AV, VenI and VenO (1)*

Moderate ICER impact

Background

- Company and the EAG adopt different preferred approaches for estimating ToT and RDI.

Company (ToT)

- AV: TTD from AMPLIFY without extrapolation.
- VenI/ VenO: TTD assumed equivalent to AV with cycle adjustment.
- VenI: curve extended 15 total cycles for protocol differences (*see appendix).

EAG comments (ToT)

- Assuming TTD equivalence across regimens is unsupported and contradicts evidence.
- Trial data and clinical practice show distinct discontinuation patterns across AV, VenI, and VenO.
- Clinical experts: discontinuation mainly due to AEs; AV's lower toxicity suggests higher completion. Equivalence assumption likely overestimates VenI/VenO completion, inflating their costs and favouring AV.
- Base case:
  - AV: applied linear TTD decline from cycle 1 to match observed trial completion. VenI: Average of GLOW and CAPTIVATE FD. VenO: Average of CLL14 and CLL13.
- Scenarios: (1) apply AV completion rates to all arms. (2) use trial-based completion rates for VenI (GLOW) and VenO (CLL14) (*see appendix).

What are the expected completion rates for AV, VenI and VenO?

Abbreviations: AV, acalabrutinib with venetoclax; RDI, relative dose intensity; TA, technology appraisal; ToT, time on treatment; TTD, time-to-treatment discontinuation; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Moderate ICER impact

Key issue 4: Modelling of ToT and RDI for AV, VenI and VenO (2)

Company (RDI)

- AV: estimates directly from AMPLIFY; [redacted] for acalabrutinib, [redacted] for venetoclax.
- TA891 (VenI): 100% RDI assumed for VenO due to lack of public data.
- Company applied 100% RDI to VenI / VenO as no publicly available RDI data.

EAG comments (RDI)

- Questions suitability of assuming 100% RDI for VenI/VenO but lower RDI for AV.
- TA891 precedent reflects data gaps, not proof of equivalent dose intensity.
- Assuming 100% RDI for VenI/VenO likely overstates drug use → cost bias favouring AV.
- Evidence & expert opinion: VenI/VenO toxicity is ≥ than AV, making 100% RDI unlikely and lower RDI for VenI and VenO plausible.
- Applying consistent RDI assumptions across arms better reflect real-world practice and avoids unfair advantage for any treatment.
- Base case: All treatments: apply RDI of 100%.
- Scenarios: (1) Venetoclax: [redacted]% RDI in all arms. Ibrutinib/ obinutuzumab: [redacted]% (matching value reported for acalabrutinib in AV). (2) Company assumption: VenI/ VenO 100%, acalabrutinib: [redacted]%, venetoclax: [redacted]%.

What RDI should be modelled for AV, VenI and VenO?

Abbreviations: AV, acalabrutinib with venetoclax; RDI, relative dose intensity; TA, technology appraisal; ToT, time on treatment; TTD, time-to-treatment discontinuation; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Key issue 5: Choice of health state utility values used in the model (1)

Small ICER impact

Background

- HRQoL data were collected within AMPLIFY, but post-progression EQ-5D data were sparse. Company fitted an MMRM to account for repeated utility measurements and estimate PF and PD utilities. Identified Kosmas et al. (2015).

Company

- Mapped AMPLIFY EQ-5D-5L data to EQ-5D-3L and estimated utilities using MMRM approach.
- Limited post-progression AMPLIFY data: applied PF-PD decrement from Kosmas et al. (2015) to AMPLIFY PF utilities in base case.
- Explored on/off treatment values for PF but assumed equal PF utilities for on- and off-treatment.
- Applied on-treatment IV-treatment decrement from Kosmas (2015), in line with previous NICE CLL appraisals.

EAG comments

- Considers that company's approach may overestimate QoL, leading to exaggerated QALY gains.
- PF on-treatment values exceed age-matched norms, unlikely to represent real experience for CLL population.
- Assuming equal PF utilities on and off treatment ignores expected improvement once toxicity resolves.
- Risk of bias in using AMPLIFY as the primary utility source → QoL gains in early treatment may be temporary and not reflect stable long-term health states.
- Limited post-progression data in AMPLIFY with no clear PD disutility relative to PF states, requiring external adjustments → introducing additional uncertainty.

Abbreviations: EQ-5D-3L, EuroQol 5 Dimension 3 Level; EQ-5D-5L, EuroQol 5 Dimension 5 Level; HSUVs, health state utility values; IV, intravenous; MMRM, mixed model for repeated measures; PF, progression-free; PD, progressed disease; QoL, quality-of-life.

Key issue 5: Choice of health state utility values used in the model (2)

Small ICER impact

EAG comments continued

- Company provided mixed-model outputs but key methodological elements remain unclear (covariates included, covariance structure applied and handling of missing data) → unclear if baseline HRQoL drivers were properly adjusted for.
- Base case: use HSUVs from Kosmas et al. (2015), values consistent with expected population norms.
- Scenario analysis: (1) utilities from AMPLIFY but limited to age-matched population norms, (2) company's original AMPLIFY-based method without age-norm caps.

Model health state	Company Base case HSUVs	Source (Relative decrements are vs PF on-treatment oral)	EAG base case mean HSUVs from Kosmas et al. (2015)
PF on-treatment (oral treatment)	[redacted]	AMPLIFY trial	**0.71**
PF on-treatment (IV treatment)	[redacted]	Kosmas relative decrement (-6%)	0.67
PF off-treatment	[redacted]	AMPLIFY trial PF on treatment value	**0.82**
PD on-treatment	[redacted]	Kosmas relative decrement (-22.5%)	0.55
PD off-treatment	[redacted]	Kosmas relative decrement (-16.9%)	0.66

Which source is most appropriate for deriving HSUVs?

Abbreviations: HRQoL: health-related quality-of-life; HSUVs, health state utility values; IV, intravenous; PF, progression-free; PD, progressed disease; QALY, quality-adjusted life year; QoL, quality-of-life.

Moderate ICER impact

Key Issue 6: Proportion and distribution of subsequent treatments (1)

Background

- Due to immature trial data, assumptions are needed to model subsequent treatments.

Company

- Assumes nearly all progressed patients across AV, VenI and VenO get subsequent therapy.

Proportion:

- Applied subsequent treatment costs to all in PD state, assuming around [redacted] receive second-line therapy.

Distribution:

- Based on UK expert estimates; assumed higher real-world use than trial data due to immaturity.
- Assumed sequencing doesn't affect post-progression survival.

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

Abbreviations: AV, acalabrutinib and venetoclax; PD, post-progression; VenI, venetoclax and ibrutinib; VenO, venetoclax and obinutuzumab.

Moderate ICER impact

Key Issue 6: Proportion and distribution of subsequent treatments (2)*

EAG comments

Proportion:

- [redacted] subsequent therapy uptake inconsistent with trial data: AMPLIFY [redacted], GLOW 7.5%, CLL14 18.1%.
  - EAG advisers: [redacted] too high, trial rates too low due to limited follow-up → balanced estimate needed.
- Subsequent therapy initiation should start at PD state transition in model (cycle 2 instead of cycle 1).
- Base case: use midpoint between trial-reported rates and progression rates of each arm to estimate overall subsequent therapy uptake. (*See appendix for EAG base case).

Distribution:

- Underrepresentation of VenR and overrepresentation of monotherapies → underestimates subsequent treatment costs:
  1. Ibrutinib initiation is rare in UK clinical practice → assign minimal proportion.
  2. Acalabrutinib is dominant BTKi; zanubrutinib use increasing but below acalabrutinib.
  3. Ven-mono exaggerated (monotherapy only for frail patients); VenR preferred for stronger responses.
- Base case: use revised distribution based on EAG adviser feedback. (*See appendix for EAG base case).
- Scenario analysis: 1) apply company's original approach, 2) estimate subsequent therapy proportions using relayed trial values.

What is the expected proportion and distribution of subsequent treatments?

Abbreviations: AV, acalabrutinib and venetoclax; BTKi, Bruton tyrosine kinase inhibitor; PD, post-progression; VenI, venetoclax and ibrutinib; VenO, venetoclax and obinutuzumab; VenR, venetoclax and rituximab.

Key issue 7: Extending consideration to people with untreated CLL with 17p deletion or TP53 mutation

Unknown ICER impact

Background

- MA includes all people with untreated CLL: people without 17p deletion or TP53 mutation (90-95%) and those with the mutation (10%).

Company

- Narrowed to those without mutation to align with AMPLIFY.
- Did not find evidence that deletion or mutation status acts as an effect modifier for fixed-duration treatments.

EAG comments

- Did not undertake analysis in subgroup with 17p deletion or TP53 mutation.
- EPAR: benefits of the proposed regimens can likely be extrapolated to this subgroup based on evidence from other studies (ELEVATE-TN, CLL14, SAT).
- Consider whether this topic decision should be applied in this subgroup to broaden treatment options allowing access for those who might otherwise miss out, simplify clinician decision-making and avoid repeat appraisals.
- Evidence for subgroup without mutation/ deletion required to evaluate efficacy and cost-effectiveness.

Other considerations

- Acalabrutinib (TA689) and venetoclax (TA796) as monotherapies are included among existing NICE recommended treatment options for untreated CLL with 17p deletion or TP53 mutation (appendix).

NICE

Is it appropriate to extend the recommendation to include individuals with the deletion or mutation?

Abbreviations: AV, acalabrutinib and venetoclax; EPAR, European public assessment report; TA, technology appraisal; TP53, tumour protein p53.

Summary of company and EAG base case assumptions (1)

Assumption	Company base case	EAG base case
Model starting age (Key issue 2)	59.9 years.	71 years.
RDI (Key issue 4)	Acalabrutinib: [redacted]%, venetoclax: [redacted]%, VenI and VenO assumed 100%.	100% for all treatments.
Proportion of Patients Completing Treatment (Key issue 4)	• AV: TTD from AMPLIFY without extrapolation • VenI/ VenO: TTD assumed equivalent to AV.	• AV: applied linear TTD decline from cycle 1 to match observed trial completion. • VenI: average of GLOW and CAPTIVATE FD. • VenO: average of CLL14 and CLL13.
HSUVs Used in Model (Key issue 5)	HSUVs derived EQ-5D from AMPLIFY, mapped and modelled using MMRM; application of PD–PF decrement from Kosmas et al. (2015) and IV-treatment decrement applied.	HSUVs from Kosmas et al. (2015).
Proportions and distribution of subsequent treatments (key issue 6)	• Applied subsequent treatment costs to all in PD state ([redacted]%). • Modelling: subsequent treatment initiated from cycle 1.	• Midpoint between trial value and proportion of patients who progressed. • Modelling: subsequent treatment initiated from cycle 2.

Abbreviations: AV, acalabrutinib and venetoclax; HSUVs, health state utility values; PD, post-progression; PF, progression free; RDI, relative dose intensity; TTD: time to treatment discontinuation; VenI, venetoclax and ibrutinib; VenO, venetoclax and obinutuzumab.

Summary of company and EAG base case assumptions (2)

Assumption	Company base case	EAG base case
TTP, Pre-PS, and PPS curves assumed equal across interventions and use the same survival curve calculations in the Markov model	Use the same survival curve calculations so TTP, Pre-PS, and PPS identical across interventions in both the base case and PSA.	Maintain assumption of equal TTP, Pre-PS, and PPS across interventions, but allow independent variation in each PSA iteration to explore uncertainty in assumption.

Company and EAG positions for non-model issues

Assumption	Company base case	EAG base case
Relevant comparators	Consider relevant comparators to be VenI and VenO (FD treatments) and exclude acalabrutinib and zanubrutinib (TTP therapies).	Acalabrutinib and Zanubrutinib monotherapies are used at 1L for CLL in people who would get AV and are relevant comparators.
Population	Seeking reimbursement in non-high risk untreated CLL.	Any NICE recommendation should consider people with high-risk untreated CLL (with mutation).

Abbreviations: 1L, first-line; FD, fixed duration; PF, progression free; PPS: post-progression survival; Pre-PS: pre-progression survival; PSA, probabilistic sensitivity analysis; TTD: time to treatment discontinuation; ToT, time on treatment; TTP: time to progression; VenI, venetoclax and ibrutinib; VenO, venetoclax and obinutuzumab. .

Cost-effectiveness results

Confidential discounts for comparators – ICERs in Part 2 slides

ICER ranges presented below

Summary:

- In the company base case AV is dominant over VenI and VenO.
- In the EAG base case AV is dominant versus VenI and VenO (excluding comparator discounts).
- EAG notes that the cost-effectiveness results should be interpreted with caution due to the assumption of equivalence.
- EAG explored uncertainty in scenarios analyses which generated ICERs above the WTP threshold in some scenarios.
- The evaluation does not meet the criteria for a severity modifier.

Abbreviations: AV, acalabrutinib and venetoclax; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life years; WTP, willingness-to-pay threshold.

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Managed access

- Company considers latest interim analysis of AMPLIFY trial to provide sufficiently mature and reliable evidence to support recommendation for AV via routine commissioning.
- Company's managed access proposal:
  - Key data sources expected to address any clinical uncertainty are the ongoing AMPLIFY trial (until [redacted]) and real-world evidence from the SACT dataset.
  - No barriers or ethical concerns for a managed access agreement have been identified.

Clinical uncertainty	Outcome data	Data source
Long-term efficacy of AV	• OS and PFS data with longer follow-up	AMPLIFY trial
Generalisability of AMPLIFY trial to UK clinical practice	• Baseline characteristics of patients receiving AV in UK clinical practice	SACT

- The managed access team considers this to have moderate potential for managed access. *See appendix for summary.

Abbreviations: AV, acalabrutinib with venetoclax; FD, fixed-duration; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

Uncaptured benefits

- Company:
  - IV-related utility decrement for VenO to be insufficient to capture the full burden of IV treatment on patients and NHS capacity, contributing to minimal QALY differences.
  - AV has better safety and tolerability than VenI and VenO, supported by company expert input, but these benefits are not reflected in QALY outputs as modelled utility decrements for AEs are small.
- EAG:
  - Company claims are not supported by robust comparative HRQoL or patient-reported data and rely largely on potentially biased company-led expert opinion.
  - IV-related utility decrement rationale is reasonable, but insufficient evidence to support model changes.

Abbreviations: AEs, adverse events; AV, acalabrutinib with venetoclax; HRQoL: health-related quality-of-life; IV, intravenous; QALY, quality-adjusted life-year; VenO, venetoclax with obinutuzumab.

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

*Under the equivalence assumption, ICERs are most sensitive to cost changes

N	Issue	ICER impact
1	Lack of comparison to acalabrutinib and zanubrutinib treat-to-progression monotherapies	Unknown
2	Generalisability of AMPLIFY trial age and fitness to target NHS population	Small
3	Reliance on assumption of equal efficacy for AV, VenI and VenO	Unknown
4	Modelling of time-on-treatment and relative dose intensity for AV, VenI and VenO	Moderate
5	Choice of health state utility values used in the model	Small
6	Proportion and distribution of subsequent treatments	Moderate

Other issues

N	Issue	ICER impact
7	Extending consideration to people with untreated CLL with 17p deletion or TP53 mutation	Small

 Abbreviations: AV, acalabrutinib with venetoclax; CLL, chronic lymphocytic leukaemia; TP53, tumour protein p53; VenI, venetoclax with ibrutinib; VenO, venetoclax with obinutuzumab.

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

Supplementary appendix

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AMPLIFY dosing regimen

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Patients with untreated CLL without a del(17p) or TP53 mutation, ECOG PS 0-2.

Population

Randomization 1:1:1

AV (arm A, n= 291)

- Acalabrutinib: 100 mg orally twice daily from Day 1 of Cycle 1 to Day 28 of Cycle 14 (continuous 28-day cycles).
- Venetoclax: 20 mg orally once daily from Day 1 of Cycle 3, with a 5-week ramp-up to 400 mg by Day 1 of Cycle 4; then 400 mg once daily to Day 28 of Cycle 14.

AVO (arm B, n=286)

- Same AV doses as Arm A
- Plus, obinutuzumab 1000 mg IV on Days 1, 2, 8, 15 of Cycle 2, then Day 1 of Cycles 3 and 7

IC of FCR or BR chemoimmunotherapy (Arm C, n=290)

- 50% received FCR and 50% received BR.
- FCR regimen: fludarabine 25 mg/m² IV + Cyclophosphamide 250 mg/m² IV, Days 1–3, Cycles 1–6 plus rituximab 375 mg/m² IV on Day 1 of Cycle 1, increasing to 500 mg/m² IV on Day 1 of Cycles 2–6
- BR regimen: bendamustine 90 mg/m² IV, Days 1–2, Cycles 1–6 plus same rituximab dosing as FCR regimen

Interventions

Comparator

Abbreviations: AV: acalabrutinib with venetoclax; AVO: acalabrutinib with venetoclax and obinutuzumab; BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance-status; FCR: fludarabine with cyclophosphamide and rituximab; IC. Investigator's choice; IV, intravenous.

SACT Data Overview*

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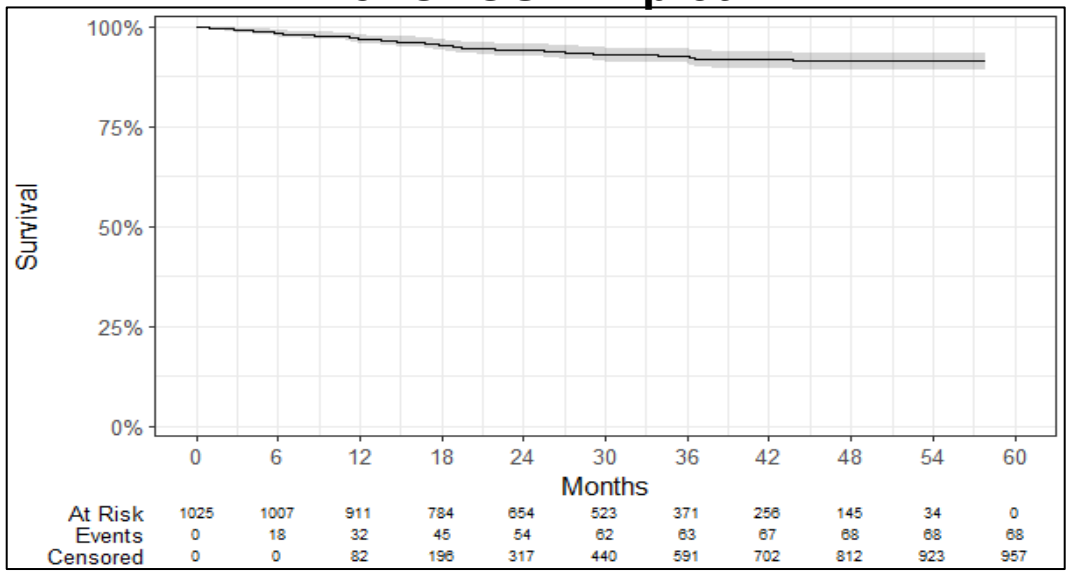
EAG requested SACT data on real-world treatment start age and OS in CLL

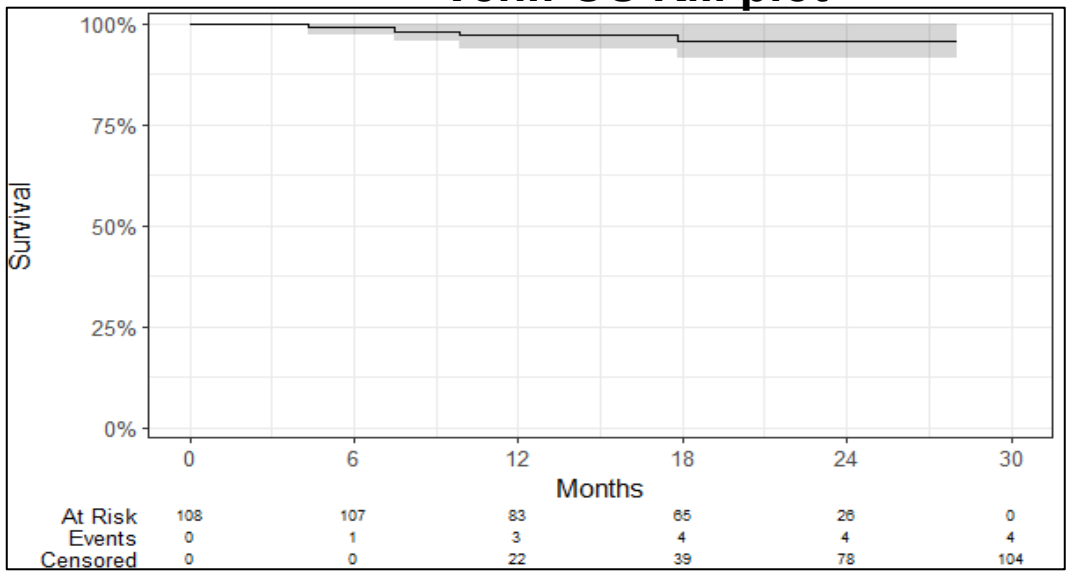
- Report was produced in partnership by the NDRS and NICE and is based on routinely collected NHS data, submitted by trusts to the SACT dataset to support understanding of current clinical practice.
- 2 Cohorts: Adults with untreated chronic lymphocytic leukemia (unknown mutation status) who have received (1) VenO or (2) VenI (*see next slides for inclusion/ exclusion flow charts for VenO and VenI).
- Outcomes: (1) Demographic and survival information and (2) OS Kaplan-Meier plot.

		VenO (N=1025)		VenI (N=108)	
Sex		Female N = 310	Male N = 715	Female N = 33	Male N = 75
Age at start of regimen	**Mean, (SD)**	64, (10)	65, (10)	66, (9)	62, (10)
	Median (Q1, Q3)	65 (57, 73)	65 (58, 72)	67 (59, 71)	63 (57, 68)

VenO: OS KM plot



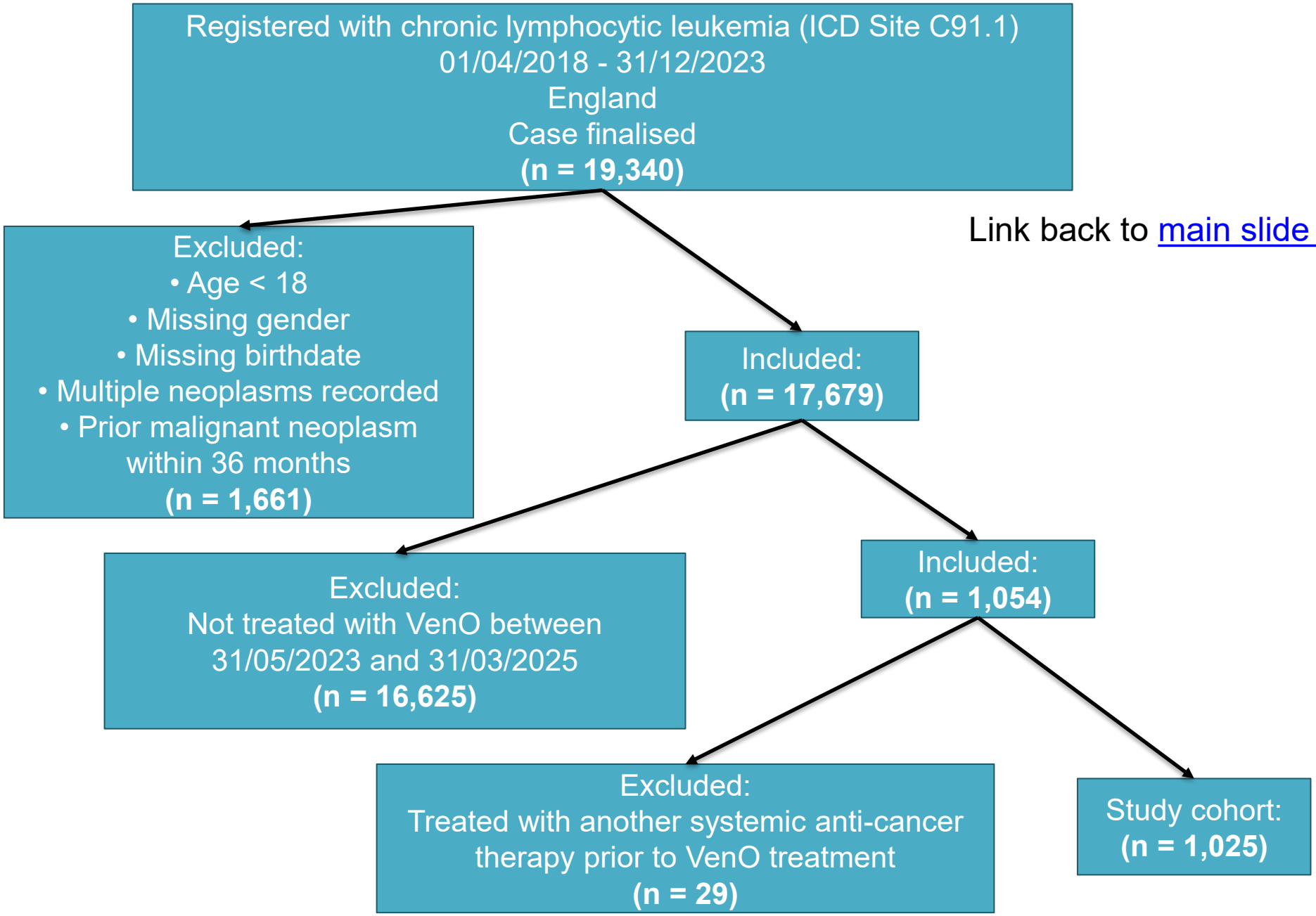
VenI: OS KM plot



NICE

Abbreviations: NDRS, National Disease and Registration Service; OS, overall survival; SACT, Systemic Anti-Cancer Therapy; VenI, venetoclax and ibrutinib; VenO, venetoclax and obinutuzumab.

Inclusion/exclusion flow chart for VenO



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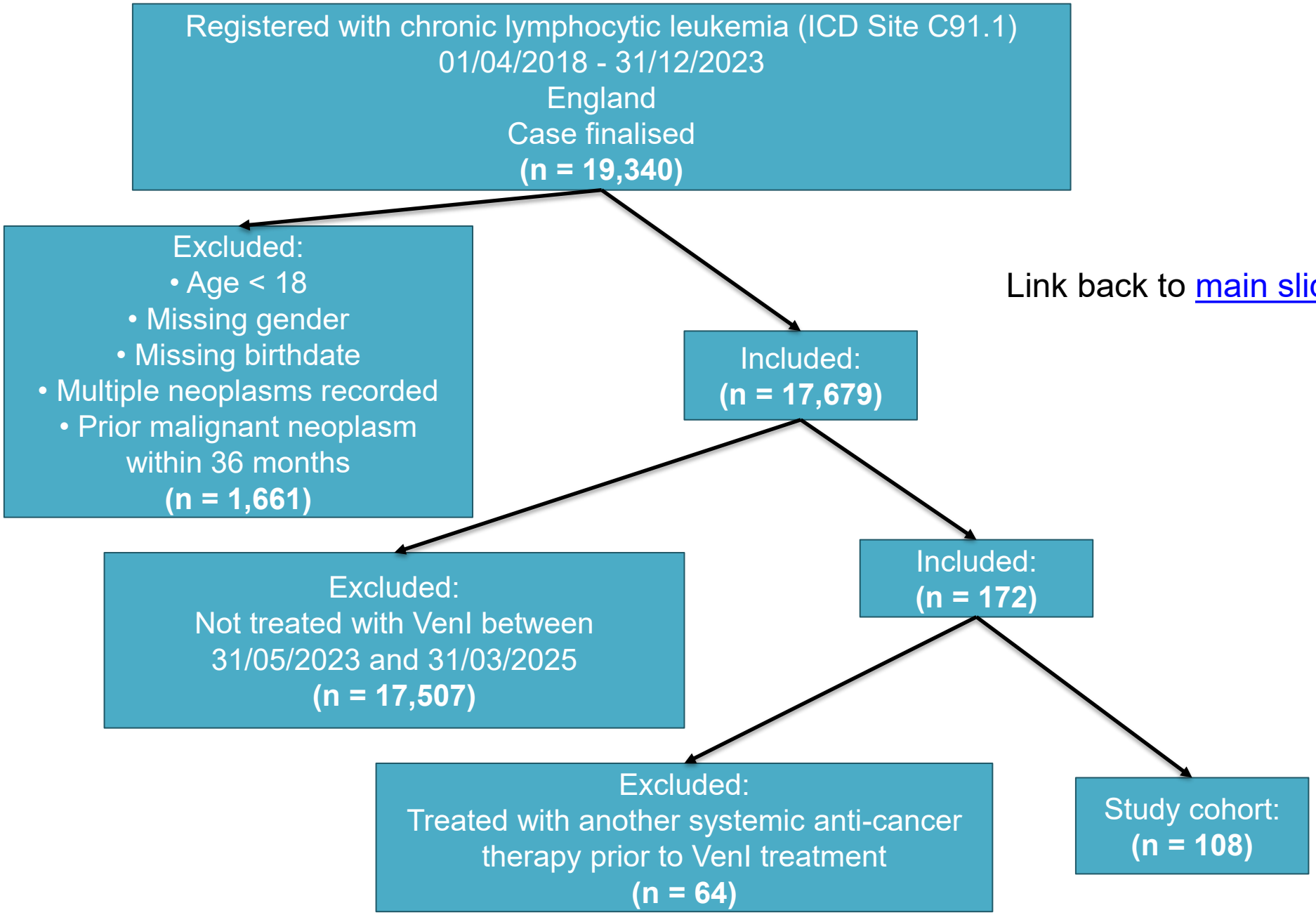
Inclusion/exclusion flow chart for VenI



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SACT Data – EAG analysis

Note: company did not provide analysis or critique of SACT data.

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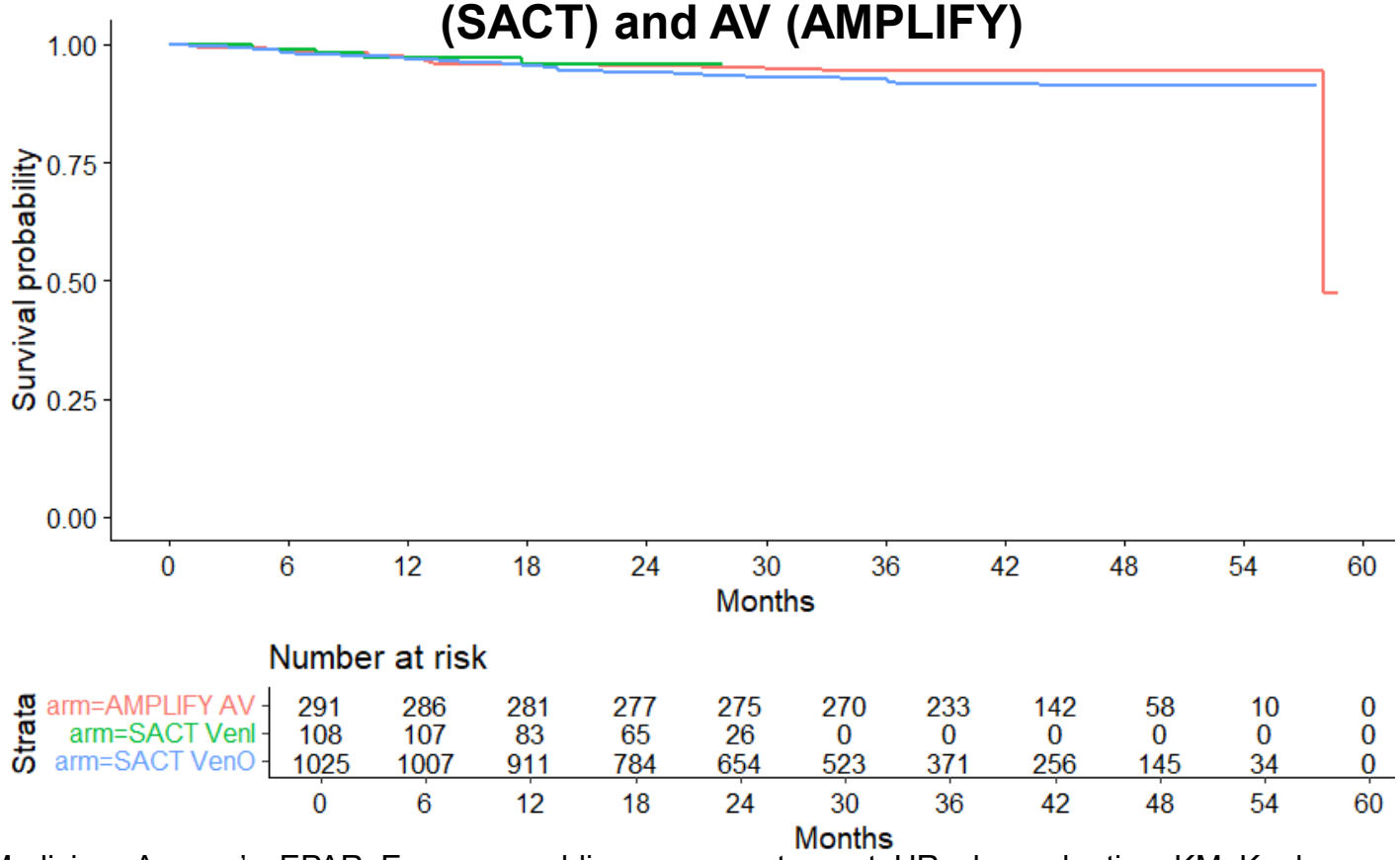
Eligibility:

- SACT VenO/VenI populations reflect a broader real-world cohort aligned with EMA EPAR guidance and MA for AV, whereas AMPLIFY applied stricter eligibility criteria → AMPLIFY represents selective, fitter patient group.

OS comparison:

- VenI and VenO reflect older, real-world populations including del(17p)/ TP53 mutation → possible bias in comparisons in favour of AV.
- KM curves look similar and Cox HRs show no significant differences vs AV (VenI: 1.11; VenO: 1.49).
- Assuming equal efficacy between VenO, VenI and AV may still favour AV.
- Did not use SACT ages:
  - different ages by sex (no clear average),
  - AV will not directly replace VenI/VenO; the NHS population may be older than SACT
  - Negligible impact given equal efficacy assumption.
- Age explored in existing EAG scenario analyses.

Comparison of OS KM functions for VenI (SACT), VenO (SACT) and AV (AMPLIFY)



Abbreviations: AV, acalabrutinib and venetoclax; EMA, European Medicines Agency's; EPAR, European public assessment report; HRs, hazard ratios; KM, Kaplan Meier; MA, marketing authorisation; OS, overall survival; SACT, Systemic Anti-Cancer Therapy; VenI, venetoclax and ibrutinib; VenO, venetoclax and obinutuzumab.

Overview of trials included in company ITC

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Study	Arm	N	Age (median)	Age >65 years (%)	Male sex (%)	ECOG PS 0–1 (%)	Rai stage III/IV (%)	Bulky disease ≥5cm (%)	CIRS >6 (%)	Creatinine clearance mL/min (median)	Beta-2 microglobulin > 3.5 mg/L (%)	TP53 mutation (%)	Del(17p) (%)	General Population Description
AMPLIFY	AV	291	61	27.1	61.2	90.0	47.1	38.8	2.1	-	58.1	0.0	0.0	No mutation
	FCR/BR	290	61	26.6	63.1	90.3	43.8	42.8	1.0	-	49.3	0.0	0.0	
CLL13	VenO	229	62	35.8	74.7	-	40.8	-	-	86.3	59.9	0.0	0.0	No mutation + Suitable for FCR/BR
	FCR/BR	229	61	34.5	71.2	-	47.1	-	-	86.3	68.0	0.0	0.0	
CLL14	OClb	216	71	-	66.2	88.4[b]	42.6[a]	-	81.9	67.4	61.8	8.3	7.3	Mutation, or No mutation + unsuitable for FCR/BR
	VenO	216	72	-	67.6	87.0[b]	43.1[a]	-	86.1	65.2	59.4	11.1	8.5	
GLOW	OClb	105	71	89.5	60	88.5[b]	52.5	36.2	58.1	63.2	73.3	1.9	0.0	Unsuitable for FCR/BR
	VenI	106	71	84.9	55.7	87.7[b]	57.3	39.0	69.8	66.5	69.8	6.6	0.0	
CAPTIVATE FD	VenI	159	60	28.0	67.0	100.0	28.0	30.0	-	-	-	10.0	13.0	Fit

NICE

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

RMST difference for OS and PFS from company STCs and Bucher ITC

	PFS			OS		
Comparison	Follow-up (months)	Distribution	RMST difference, months (95% CI)	Follow-up (months)	Distribution	RMST Difference (months) for OS
CAPTIVATE FD + GLOW						
AV vs VenI	55.1	Gompertz	[redacted]	57.7	Gompertz	[redacted]
GLOW only						
AV vs VenI	55.1	Gompertz	[redacted]	57.7	Gompertz	[redacted]
CLL14						
AV vs VenO	55.1	Gompertz	[redacted]	57.7	Gompertz	[redacted]
CLL13						
AV vs VenO (Bucher ITC)	55.1	[redacted]	[redacted]	57.1	[redacted]	[redacted]

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NICE

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

Unanchored MAIC: Patient baseline characteristics before and after matching

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Characteristic	AMPLIFY (AV) (N=291)	GLOW + CAPTIVATE (Pooled VenI IPD) (N=265)	After reweighting (N=146, ESS=101)
Age			
Median	61	65	61
≤65 years	73%	55%	73%
Unmutated IGHV	57%	61%	57%
CrCl <60 ml/min	13%	17%	13%
del11q	18%	19%	18%
Male	61%	62%	61%
Rai Stage			
0–I	17%	28%	17%
II	36%	33%	36%
III	24%	21%	24%
IV	23%	19%	23%
Bulky Disease (≥5cm)	39%	34%	39%
Median Time from Diagnosis (months)	28.5m	35.5m	26.8m
ECOG PS			
0–1	90%	95%	90%
2	10%	5%	10%

NICE Abbreviations: AV, acalabrutinib plus venetoclax; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy chain variable region; IPD, individual patient data; N, number of patients; Rai, Rai staging system; VenI, ibrutinib plus venetoclax

Proportion of patients completing treatment

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Company approach

Regimen	Drugs	Maximum treatment cycles (trial protocol)	Proportion of patients who completed treatment
Acalabrutinib + venetoclax	Acalabrutinib	14.00	[redacted]
	Venetoclax	12.00	[redacted]
Ibrutinib + venetoclax	Ibrutinib	15.00	[redacted]
	Venetoclax	12.00	[redacted]
Venetoclax + obinutuzumab	Obinutuzumab	6.00	[redacted]
	Venetoclax	12.00	[redacted]

EAG base case and scenarios

Regimen	Drugs	EAG base case: Completion (%)	EAG scenario 3: Completion (%)
Acalabrutinib + venetoclax	Acalabrutinib	[redacted]	[redacted]
	Venetoclax	[redacted]	[redacted]
Ibrutinib + venetoclax*	Ibrutinib	85.0%	77.4%
	Venetoclax	85.0%	77.4%
Venetoclax + obinutuzumab**	Obinutuzumab	84.9%	76.4%
	Venetoclax	84.9%	76.4%

NICE

*VenI completion: GLOW: 77.4% (82/106), CAPTIVATE FD: 92.5% (147/159). Average: 85.0%.

** VenO completion:CLL13: 93.4% (214/229), CLL14: 76.4% (165/216).Average: 84.9%.

Subsequent treatment distributions used in the company and EAG base case

Subsequent treatment	% of patients receiving treatment after			% of patients receiving treatment after	Rationale
	Company			EAG	
	AV	VenI	VenO		
Acalabrutinib monotherapy	[redacted]	[redacted]	[redacted]	35	Most common 2nd-gen BTKi
Ibrutinib monotherapy	[redacted]	[redacted]	[redacted]	0	Rarely initiated
Venetoclax monotherapy	[redacted]	[redacted]	[redacted]	3	For frail only
Venetoclax with rituximab	[redacted]	[redacted]	[redacted]	37	Preferred for deep response
Zanubrutinib monotherapy	[redacted]	[redacted]	[redacted]	25	Increasing use; complements Acalabrutinib

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Managed access team considerations

Uncertainty	Resolvable	Explanation and source
Long-term efficacy of AV	Yes	From AMPLIFY trial.
Generalisability of AMPLIFY trial to UK clinical practice	Yes	From SACT real-world evidence.
Proportion and distribution of subsequent treatments	Yes	Yes, from AMPLIFY trial and SACT data.
Modelling of time on treatment for VenI and VenO	No	MA doesn't usually cover comparators. Also complex to extract from SACT data as VenI and VenO are combination therapies.
Equivalence assumption	Unlikely	MA doesn't usually cover comparators. Could be explored.
Utility values	Low	No further data source
Appropriate comparators	No	Choice for committee

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Recent NICE recommendations for CLL

Appraisal	Treatment	Recommendation
TA1119	Venetoclax with obinutuzumab (VenO)	'*untreated* CLL in adults' *
TA891	Venetoclax with ibrutinib (VenI)	'*untreated* CLL in adults' *
TA931	Zanubrutinib monotherapy	'CLL in adults if • untreated and ❑ there is a 17p deletion or TP53 mutation ❑ there is no a 17p deletion or TP53 mutation, and unsuitable for FCR or BR • Relapsed or refractory'
TA689	Acalabrutinib monotherapy	'*untreated* CLL in adults if • there is a 17p deletion or TP53 mutation • there is no a 17p deletion or TP53 mutation, and unsuitable for FCR or BR'
TA796	Venetoclax monotherapy	'CLL in adults with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable'

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*irrespective of 17p deletion or TP53 mutation status;
BR, bendamustine plus rituximab; FCR, fludarabine plus cyclophosphamide

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