NHS England

Clinical Priorities Advisory Group Summary Report

Agenda item	3.7
Date of Meeting	11/05/2026-13/05/2026
Title of the Proposition	Combination brentuximab vedotin and bendamustine for patients aged 8 years and above with relapsed or refractory classical Hodgkin lymphoma
Unique Reference Number	2404
Programme of Care	Cancer
Clinical Reference Group	Chemotherapy
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommended its relative prioritisation.

Summary of the proposition:

Bendamustine and brentuximab vedotinis recommended to be available as a routine commissioning treatment option for patients aged 8 years and above with relapsed or refractory classical Hodgkin lymphoma within the criteria set out in this document.

BV is an antibody-drug conjugate which is licenced and NICE approved for use in cHL (TA524). It works by binding to a protein on the cancer cell surface (CD30) and delivers a cytotoxic molecule to the cancer cells. This stops them from dividing and the cancer cell eventually dies.

Bendamustine is an alkylating chemotherapy drug. It works by inducing DNA damage and cross-linking DNA strands, which inhibits the ability of cancer cells to grow and survive. It has demonstrated clinical efficacy in several lymphoid malignancies, including non-Hodgkin lymphoma and cHL. However, its use in the treatment of R/R cHL, as well as in combination with BV, are off-label.

Recent studies have found high response rates and SCT rates with the combination of BV with bendamustine (BVB), much higher than reported with current third-line treatments, i.e. brentuximab or pembrolizumab alone. Treatment with BVB is also shorter than BV or pembrolizumab monotherapy and reduces the need for subsequent therapies.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Cancer Programme confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒

	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Very low	This outcome is important to patients as patients with R/R HL have a higher mortality rate due to previously failed therapy. Improved overall survival is an important marker of effective treatment, although it does not provide information about a patient's health and wellbeing during that time. In total, six studies (one phase I-II trial and five case series) provided evidence relating to overall survival. *1-year overall survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R[33] classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a 1-year overall survival[34] of 85%. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R[35] CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 1-year overall survival[36] of 86%. **(VERY LOW)** *2-year overall survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a 2-year overall survival of 72%. **(VERY LOW)** At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R[37] classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported a 2-year overall survival[38] of 93%. **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL[39] receiving BVB (median prior therapy of 2 (range 1 to 4)) reported a 2-year overall survival[40] of 72%. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8))

	reported a 2-year overall survival of 82%. **(VERY LOW)** *3-year overall survival* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R[41] HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported a 3-year overall survival[42] of 75% (95% CI 59 to 95). **(VERY LOW)** *Median overall survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a median overall survival of not reached. **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported a median overall survival of not reached. **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R[43] classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported a median overall survival of not reached. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported a median overall survival of 43.3 months (95% CI 11.3 to not reached) in the phase I trial and not reached in the phase II trial. **(VERY LOW)** **Six non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for overall survival. One single arm (phase II) trial and one retrospective case series reported a 1-year overall survival of 86% at an unspecified follow-up and 85% at a median follow-up of 14 months.** **One single arm (phase II) trial and two retrospective case series reported a 2-year overall survival ranging from 72% to 82% up to a median follow-up of 19 months. One retrospective case series reported a 2-year overall survival of 93% at a median follow-up of 17 months in patients receiving BVB followed by ASCT.** **One retrospective case reported a 3-year overall survival of 75% (95% CI 59 to 95) at a median follow-up of 12 months.** **Three retrospective case series reported a median overall survival of not reached up to a median follow-up of 38 months and one single arm (phase I-II) trial reported a median overall survival of 43.3 months (95% CI 11.3 to not reached) at phase I and not reached at phase II at an unspecified follow-up.**
Response rate **Certainty of evidence:** Very low	This outcome is important to patients as it indicates the treatment has successfully been able to treat the cancer. Complete response rate is an important marker of effective treatment as it is associated with better survival outcomes and higher transplant rates. In total, seven studies (one phase I-II trial and six case series) provided evidence relating to response rate. *Overall response rate (complete and partial response)* At the end of BVB treatment with a median of three cycles (range 1 to 6): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported an overall response rate[44] of 92.6% (complete response, n (%): 29 (70.7) and partial response: 9 (21.9)) before ASCT. **(VERY LOW)** • One retrospective case series (Radhakrishnan et al 2021) (n=29) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported an overall response rate[45] of 79% (complete metabolic response, n (%): 18 (62), partial response: 5 (17), stable disease: 1 (3), progressive disease: 5 (17)). **(VERY LOW)**

	At the end of BVB treatment with a median of four cycles (range 2 to 6): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported an overall response rate of 82% (complete response rate, n (%): 42 (68.9), partial response rate: 8 (13.1), refractory rate: 11 (18)). **(VERY LOW)** At the end of BVB treatment with a median of four cycles (2.5 to 97.5 percentiles 2 to 7): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported an overall response rate[46] of 79% (95% CI 64 to 89) (complete response rate: 49%, (95% CI 34 to 64)). **(VERY LOW)** At the end of BVB treatment with up to eight cycles: • One retrospective case series (Moretti et al 2022) (n=40) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported an overall response rate[47] of 75% (95% CI 59% to 86%) (complete response rate: 50% (95% CI 35% to 66%)). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported an overall response rate[48] of 61% (95% CI 41 to 79) in the phase I trial, 78% (95% CI 62 to 91) in the phase II trial and 71% (95% CI 58 to 81) for phase I and phase II patients combined. **(VERY LOW)** *Complete metabolic response* At a median of 5 (range 5 to 6) weeks after the 4th BVB cycle: • One case series[49] (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R[50] classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that 20 (100%) of patients achieved complete metabolic response[51] (DS scores of 1: 8 patients, 2: 8 patients, 3: 4 patients). **(VERY LOW)** *Duration of response* At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported a duration of response[52] of 4.3 months (95% CI 0 to 7.1) in the phase I trial and 3.95 months (95% CI 7.5 to not reached) in the phase II trial. **(VERY LOW)** **Seven non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for response rate. One single arm (phase I-II) trial and four retrospective case series reported an overall response rate of 71% to 82% (complete response rate 49% to 68.9% where reported) at end of BVB treatment. One retrospective case series reported an overall response rate of 92.6% (complete response rate 70.7%) at end of BVB treatment in patients receiving BVB followed by ASCT.** **One case series reported that 100% of patients achieved complete metabolic response.** **One single arm (phase I-II) trial reported a duration of response of 4.3 months (95% CI 0 to 7.1) in the phase I trial and 3.95 months (95% CI 7.5 to not reached) in the phase II trial.**
Eligibility for stem cell transplant **Certainty of evidence:** Very low	This outcome is important to patients as it indicates the treatment is able to progress them safely to stem cell transplant. Progression to stem cell transplant is important as this is the definitive treatment of R/R Hodgkin lymphoma and improves overall survival. In total, five case series provided evidence relating to eligibility for stem cell transplant. *Number of patients eligible for SCT after BVB* At the end of BVB treatment with a median of three cycles (range 1 to 6): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that 28 patients were eligible for SCT[53] after BVB. **(VERY LOW)** *Number of patients undergoing SCT after BVB* At the end of BVB treatment with a median of three cycles (range 1 to 6): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and

	young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that 25 patients underwent SCT[54] (20 post BVB & 5 after subsequent regimens), 17 of which were ASCT and eight allo-SCT. **(VERY LOW)** At the end of BVB treatment with four cycles: • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that 14 patients underwent ASCT and four patients underwent allo-SCT. **(VERY LOW)** At the end of BVB treatment with a median of four cycles (range 2 to 6): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that out of 32 patients given BVB as a bridge to ASCT, 29 had ASCT and three had allo-SCT after BVB salvage; out of two patients given BVB as a bridge to allo-ASCT, two had allo-ASCT; and out of 18 patients given BVB after ASCT relapse, seven patients had allo-SCT. Nine patients were transplant ineligible due to comorbidities prior and post BVB. **(VERY LOW)** At the end of BVB treatment with a median of four cycles (2.5 to 97.5 percentiles 2 to 7): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 26 patients (17 with complete response, 7 with partial response & 2 with stable disease after BVB) proceeded to a SCT (20 ASCT, 4 allo-SCT & 2; tandem ASCT-allo-SCT). **(VERY LOW)** At the end of BVB treatment with up to eight cycles: • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that 15 (36.6%) responding patientssa underwent SCT. Nine patients underwent SCT after four cycles of BVB (7 ASCT and 2 allo-SCT) and six patients underwent SCT after ≥6 cycles of BVB (1 ASCT & 5 allo-SCT). **(VERY LOW)** **Five case series (four retrospective and one unspecified) of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence relating to eligibility for stem cell transplant. One case series reported that 28 out of 30 patients were eligible for SCT, 25 of whom underwent SCT after BVB treatment. One case series reported that out of 32 patients given BVB as a bridge to ASCT, 29 had ASCT and three had allo-SCT after BVB salvage; out of two patients given BVB as a bridge to allo-ASCT, two had allo-ASCT; out of 18 patients given BVB after ASCT relapse, seven patients had allo-SCT and nine patients were transplant ineligible due to comorbidities prior and post BVB. The remaining three case series reported that 26 out of 47, 15 out of 41 and 18 out of 20 patients underwent SCT after BVB.**
Important outcomes	
Event-free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time during which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, one case series provided evidence relating to event free survival. *3-year event-free survival* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had two or more treatment lines prior to BVB) reported 3-year event-free survival of 58% (95% CI 37 to 90). **(VERY LOW)** **One retrospective case series of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty of 3-year event-free survival of 58% (95% CI 37 to 90) at a median follow-up 12 months.**
Progression-free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, seven studies (one phase I-II trial and five case series) provided evidence relating to

	progression-free survival. *1-year progression-free survival* At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 1-year progression-free survival[55] of 67%. **(VERY LOW)** *2-year progression-free survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a 2-year progression-free survival[56] of 60%. **(VERY LOW)** At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported a 2-year progression-free survival[57] of 62%. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported a 2-year progression-free survival[58] of 93.7% (95% CI 62.7 to 99.6). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 2-year progression-free survival[59] of 62%. **(VERY LOW)** *Median progression-free survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a median progression-free survival of 26 months (95% CI 13.9 to 38). **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported a median progression-free survival[60] of 18 months (95% CI 4.5 to 31.4). **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported a median progression-free survival[61] of 26 months (95% CI 7.2 to not reached). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported a median progression-free survival of 7.5 months (95% CI 4.8 to 12.1) in the phase I trial and not reached in the phase II trial. **(VERY LOW)** **Seven non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for progression-free survival.** **One single arm (phase II) trial reported a 1-year progression-free survival of 67% at an unspecified follow-up.** **One single arm (phase II) trial and two retrospective case series reported a 2-year progression-free survival ranging from 60% to 93.7% up to a median follow-up of 27 months. One retrospective case series reported a 2-year progression-free survival of 62% at a median follow-up of 17 months in patients receiving BVB followed by ASCT.** **One single arm (phase I-II) trial reported a median progression-free survival of 7.5**

	months in the phase II trial and not reached in the phase II trial at an unspecified follow-up and three retrospective case series reported a median progression-free survival of 18 to 26 months up to a median of 38 months follow-up.
Disease-free survival or remission **Certainty of evidence:** Not applicable	This outcome is important to patients as it means that the signs and symptoms of cancer have reduced, either partially or completely and they are free of all detectable disease. **No evidence was identified for this outcome.**
Quality of life **Certainty of evidence:** Not applicable	This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Treatment related impacts on specific quality of life measures are also useful for this purpose. **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, seven studies (one phase I-II trial and six case series) provided evidence relating to safety. *Adverse events (AEs) of any grade* At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that 24 (58.5%) patients experienced treatment-related AEs of any grade. The most common AEs were neutropenia (17%), peripheral neuropathy (12.2%) and infusion-related reactions with fever, chills, flushing, or pruritus (12.2%). **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that 19 (46%) patients experienced treatment emergent AEs of any grade. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on toxicities of any grade. In the phase I trial, the most common toxicities (>25%) were, n (%): nausea 15 (54%), vomiting 10 (36%), dyspnoea 10 (36%), peripheral sensory neuropathy 9 (32%), diarrhoea 8 (29%), pruritus 8 (29%), cough 8 (29%), constipation 7 (25%), and fever 7 (25%). In the phase II trial, the most common AEs (>25%) were, n (%): fatigue 25 (68%), nausea 25 (68%), fever 15 (41%), diarrhoea 14 (38%), vomiting 12 (32%), and rash maculopapular 12 (32%). **(VERY LOW)** *Grade 1 AEs* At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 1 toxicities, n (%). • Phase I: chills 6 (21%), diarrhoea 6 (21%), pain 6 (21%), dysguesia 5 (18%), dyspnoea 5 (18%), fatigue 5 (18%), fever 5 (18%), nausea 5 (18%), constipation 4 (14%), cough 4 (14%), headache 4 (14%), abdominal pain 4 (14%), dyspepsia 4 (14%), pruritus 4 (14%), rash maculopapular 3 (11%), back pain 3 (11%), hot flashes 3 (11%), hyperhidrosis 3 (11%), nasal congestion 3 (11%), sore throat 3 (11%), vertigo 3 (11%), anxiety 2 (7%), vomiting 2 (7%) and infusion-related reaction 1 (4%). • Phase II: nausea 20 (54%), diarrhoea 10 (27%), fatigue 10 (27%), dyspnoea 8 (22%), headache 7 (19%), constipation 6 (16%), cough 6 (16%), pain 6 (16%), rash maculopapular 6 (16%), fever 5 (14%), vomiting 5 (14%), dysguesia 4 (11%), dyspepsia 4 (11%), chills 3 (8%), vertigo 3 (8%), anxiety 1 (3%), myalgia 2 (5%) and nasal congestion 2 (5%). **(VERY LOW)**

	Grade 2 AEs At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 2 toxicities, n (%). • Phase I: fatigue 10 (36%), nausea 10 (36%), peripheral sensory neuropathy 9 (32%), vomiting 8 (29%), cough 4 (14%), pruritus 4 (14%), diarrhoea 2 (7%), constipation 3 (11%), fever 2 (7%), dyspnoea 5 (18%), and anxiety 1 (4%). • Phase II: fatigue 15 (41%), fever 10 (27%), vomiting 7 (18%), pruritus 6 (16%), rash maculopapular 6 (16%), nausea 5 (14%), lung infection 5 (14%), diarrhoea 4 (11%), abdominal pain 4 (11%), infusion-related reaction 4 (11%), back pain 2 (5%), anaemia 2 (5%), peripheral sensory neuropathy 2 (5%), and constipation 1 (3%). **(VERY LOW)** *Grade 3 AEs* At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that 3 (7.3%) patients experienced grade 3 AEs. These were n (%): neutropenia (2 (4.8%)) and peripheral neuropathy (1 (2.4%)). **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported on the number of patients experiencing grade 3 treatment emergent AEs. These were, n (%): infections (3 (7%); 1 with CMV pneumonia, and H1N1 pneumonia, 1 with CMV pericarditis and 1 with sepsis caused by Klebsiella pneumoniae neutropenic fever), neutropenia (3 (7%)), peripheral neuropathy (2 (5%)) and febrile neutropenia (1 (2%)). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 3 toxicities. For phase I these were, n (%): anaemia 5 (18%), platelet count decreased 4 (14%), neutropenia 3 (11%), and infusion-related reaction 2 (7%). For phase II these were, n (%): neutropenia 10 (27%) and lung infection 5 (14%). **(VERY LOW)** *Grade 3 or 4 AEs* At a median follow-up 12 months (95% CI 5.2 to 18.8)[62]: • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported on number of patients experiencing grade 3 or 4 treatment related adverse events. These were, n (%): neutropenia 21 (70%; grade 3 (28 of 92 cycles of BVB administered (30.4%)) & 1 grade 4), peripheral neuropathy 4 (13%), clinically detected infection 4 (13%), mucositis 3 (10%), skin rash 2 (6.5%) and liver/hepatitis 2 (6.5%). **(VERY LOW)** At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported on number of patients experiencing grade 3 or 4 AEs. These were, n (%): lymphopenia 25 (40%), neutropenia 15 (24.6%), thrombocytopenia 8 (13.1%), anaemia 8 (13.1%), infusion reaction 5 (8.2%), vomiting 3 (4.9%), neuropathy 4 (6.5%) and skin reactions 2 (3.2%). **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5)[63]: • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 15 (34%) patients experiencing grade >3 AEs. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that 10 (50%) patients experienced grade 3 or 4 treatment related

	adverse events. **(VERY LOW)** *Grade 4 AEs* At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that no patients experienced grade 4 AEs. **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that no patients experienced grade 4 toxicities. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 4 toxicities. For phase I there were no grade 4 toxicities and for phase II there were 3 (8%) patients experiencing grade 4 neutropenia. **(VERY LOW)** *Infusion reactions* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that 12 (40%) patients experienced grade 1 or 2 infusion reactions. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that two (10%) patients experienced serious infusion related reactions. **(VERY LOW)** *Discontinuation of treatment due to AEs* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that no patients experienced discontinuations or treatment delays due to BVB toxicity. **(VERY LOW)** At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that 10 (16.4%) patients experienced drug cessation due to AEs. **(VERY LOW)** At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that one patient discontinued bendamustine due to severe, treatment-related neutropenia. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that eight (40%) patients temporarily discontinued therapy due to treatment-related AEs. **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that one patient discontinued therapy due to febrile neutropenia and diarrhoea after the first cycle. **(VERY LOW)** *Interrupting treatment due to grade 4 toxicity* At a median follow-up of 19 months (95% CI 17.4 to 18.5)[64]:

	• One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 11% of patients experienced interrupting treatment due to grade 4 toxicity. **(VERY LOW)** *Lower drug doses due to AEs* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that two (3.3%) patients had lower drug doses due to AEs. **(VERY LOW)** **One single arm (phase I-II) trial and five case series of R/R HL patients receiving BVB as third or subsequent line treatment and one case series of R/R HL patients receiving BVB as third or subsequent line treatment followed by ASCT provided very low certainty evidence relating to safety.** **Any grade AEs. One case series reported that just under half of patients (46%) experienced treatment related AEs of any grade at a median of 38 months follow-up and one case series of patients receiving BVB followed by ASCT reported that just over half (58.5%) experienced any grade AEs.** **One single arm (phase I-II) trial and one case series reported the following most common grade 3 AEs: neutropenia (7% & 27%), anaemia (18%), infection (7% & 14%) and thrombocytopenia (14%) at a median follow-up of 38 months or unspecified follow-up. Two case series reported that 15 (34%) patients at a median follow-up of 19 months and 50% at a median follow-up of 27 months experienced grade 3 or 4 AEs. Two further case series reported the following most common grade 3 or 4 AEs: neutropenia (24.6% & 73%), lymphopenia (40%), thrombocytopenia (13.1%), anaemia (13.1%), peripheral neuropathy (13%) and clinically detected infection (13%) at a median follow-up of 12 and 14 months. One single arm trial and three case series reported on grade 4 AEs up to a median follow-up of 38 months. One study reported no grade 4 AEs and two studies reported cases of grade 4 neutropenia (3 (8%) patients & 1 patient). One case series of R/R HL patients receiving BVB followed by ASCT reported that 7.3% of patients experienced grade 3 AEs (neutropenia (4.8%) and peripheral neuropathy (2.4%)) and no patients experienced grade 4 AEs at a median follow-up of 17 months.** **Four case series of R/R HL patients receiving BVB as third or subsequent line treatment and one case series of R/R HL patients receiving BVB as third or subsequent line treatment followed by ASCT reported on discontinuation of therapy due to treatment-related AEs, with results ranging from 0% to 40% up to a median follow-up of 38 months. One case series reported on the interruption of treatment due to grade 4 toxicity, with 11% of patients affected at a median follow-up of 19 months. One case series reported that 3.3% of patients had lower drug doses due to AEs at a median follow-up of 14 months.**
Abbreviations AEs: adverse events; allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BVB: brentuximab vedotin and bendamustine; CD30: cluster of differentiation 30; CI: confidence interval; CMV: cytomegalovirus; DS: Deauville score; HL: Hodgkin lymphoma; R/R: relapsed or refractory; SCT: stem cell transplant	

Patient Impact assessment

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients may have slight problems in walking about
- **ability to provide self-care:** Patients may be unable to wash or dress
- **undertaking usual activities:** Patients may be unable to do their daily activities
- **experience of pain/discomfort:** Patients may have moderate pain or discomfort

• **experience of anxiety/depression:** Patients are extremely anxious or depressed
Further details of impact upon patients: Classical Hodgkin Lymphoma can cause distressing symptoms such as fatigue, night sweats and fevers that can affect patients' abilities to go to work or school and engage with everyday life. Although first line treatment is generally successful, treatment can be disruptive, side effects can be incredibly distressing, and daily activities can be incredibly difficult having severe implications on patients' mental health. Patients may suffer from anxiety and low mood when facing uncertainty about their future treatment options or disease progression. **Further details of impact upon carers:** Patients may require additional support with normal activities and functioning whilst dealing with their symptoms, which may severely impact on their care giver's mental health and cause severe anxiety or depression. Though many respond well, patients may require additional support during treatment and periods of relapse which can put strain on carers. Additionally, patients undergoing treatment may suffer from side effects such as infection, full body rash and confusion which can be distressing for patients and their families.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This policy proposition aims to provide a third-line or subsequent treatment for patients of all ages with relapsed or refractory classical Hodgkin lymphoma. The policy proposition is not thought to adversely impact on any individuals from protected characteristic groups. However, one of the benefits of treatment with brentuximab vedotin and bendamustine is that a reduced number of treatment cycles is required which will be beneficial to individuals and their families from protected characteristic groups and on those experiencing health inequalities.
13Q Assessment	
PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes

Rare Disease Advisory Group

Not Applicable

Pharmaceutical

Yes

The Clinical Commissioning Policy Proposition recommends the combination use of brentuximab vedotin and bendamustine as a treatment option in people aged 8 years and over with relapsed or refractory classical Hodgkin lymphoma. This recommendation is outside the marketing authorisations for brentuximab vedotin and bendamustine, so use is off-label. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined, using separate prior approval forms for registration of adults and children.

Both drugs are included on the NHS Payment Scheme Annex A, so are high-cost drugs; however, bendamustine is reimbursed within the fixed ‘block’ allocation.

National Programme of Care

The proposal received the full support of the Cancer National Programme of Care.