Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp

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(Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp. 2010. University of Exeter. (Report)

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Martin Hoyle	Critiqued the model provided by industry and wrote the economic evaluation chapter
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1 SUMMARY

Indented, italicised, 1.5 line spaced sections of text have been copied from the submission by Napp, hereafter referred to as 'the submission'. References which appear within this text within square brackets refer to those cited in the Napp submission, the evidence review group (ERG) have also added a note of first author and year.

1.1 Scope of the submission

The submission from Napp considers the use of bendamustine for the first-line treatment of chronic lymphocytic leukaemia (CLL) (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

The comparator in the submission was chlorambucil, the current standard first-line therapy for patients not suitable for a fludarabine-containing regimen. The pivotal, Phase III randomised study provides a direct comparison of bendamustine with chlorambucil.

The clinical effectiveness outcomes considered are: progression-free survival (PFS), response rates, overall survival (OS), adverse effects (AEs) of treatment; and, health-related quality of life (HRQL). The outcomes for the economic evaluation were: The time horizon used for the economic analysis was 35 years, and costs were considered from an NHS and Personal Social Services (PSS) perspective.

The scope of the manufacturer's submission is consistent with the components of the question and approach outlined in the final scope.[1]

1.2 Summary of submitted clinical effectiveness evidence

The submission from Napp includes one study, 02CLLIII; a Phase III, open-label, randomised, parallel group, multicentre, international study. In accordance with the licensed indication, this study compares bendamustine directly with chlorambucil in patients with previously untreated B-CLL (at Binet stage B or C), who were considered not suitable for fludarabine-based therapy.

Of the 319 participants recruited, 162 were randomised to bendamustine and 157 patients randomised to chlorambucil. Patients' response to the treatment was assessed according to criteria defined by the National Cancer Institute Working Group on CLL[2][3] and had to be met for at least eight weeks. After the last treatment cycle, patients were monitored for response and survival at three-month intervals. Final assessment of best response was performed in a blinded fashion by an Independent Committee for Response Assessment (ICRA) and classified as Complete Response (CR), Partial Response (PR), PR with nodular involvement, stable disease (SD), or progressive disease PD). Secondary endpoints included time to progression, duration of remission, and overall survival. Safety endpoints were infection rates and adverse events.

In Study 02CLLIII, patients receiving bendamustine had a higher overall response rate (ORR) than those in the chlorambucil group (68% vs 31%; P<0.0001). The median PFS was also significantly longer with bendamustine than with chlorambucil (21.6 months vs 8.3 months; P<0.0001).

Adverse events were reported in 89% of patients in the bendamustine group and 81% of the chlorambucil group, with the most common being haematologic in nature. Severe infections of Grade 3 or 4 occurred in 8% and 3% of treated patients in the bendamustine and chlorambucil arm, respectively, with one singular Grade 4 infection in the chlorambucil arm. In general, these events are consistent with those expected in this population of people with CLL.

1.3 Summary of submitted cost effectiveness evidence

Napp used a cohort-based cost-effectiveness model to project expected clinical and economic outcomes for patients for whom fludarabine combination chemotherapy is not appropriate receiving either bendamustine or chlorambucil. The model is of high quality. Broadly speaking, the structure of Napp's model is typical of models for cancer, in that the health states Progression Free Survival (PFS) and Progressive Disease (PD) are modelled. However, it is more sophisticated than some models for the following two reasons;

- PFS is split according to response: CR, PR or SD. The depth of response influences the utilities (better responses having higher utility) and the disease-management costs (better responses carrying lower costs).

- re-treatment with first line therapy and subsequent second line fludarabine combination (FC) therapy is modelled. This reflects the reality of management, in which improvement on initial therapy may permit subsequent use of FC.

Napp's base case ICER for bendamustine vs. chlorambucil is **£12,000 per QALY**. When we update Napp's model with assumptions that we believe are more appropriate, the ICER decreases to **£9,400 per QALY**.

Napp estimate the cost-effectiveness of bendamustine for the following subgroups as;

- Patients age ≥ 65   ICER = £12,600 per QALY

- WHO ≥ 1   ICER = £13,500 per QALY

- Patients age ≥ 65, and WHO ≥ 1   ICER = £13,600 per QALY.

It was not possible to confirm these ICERs because there is no independent source with which to check the subgroup-specific response data and survival curves. Also, the ERG has not explored alternative ICERs for the subgroups because it did not have updated estimates for the hazard ratios by subgroup for OS.

1.4   Commentary on the robustness of submitted evidence

1.4.1 Strengths

- Study 02CLLLIII is of good quality which reflects UK clinical practice.

- The searches performed are appropriate and include all relevant studies.

- Overall, the ERG considers that the economic model is of high quality.

- The ERG found no logical errors in their model.

- The manufacturer has taken steps to increase the realism of their model by splitting PFS in to SD, PR and CR, and by modelling re-treatment with first line therapy and subsequent second line FC therapy.

1.4.2 Weaknesses

- Study 02CLLIII is an open-label study and therefore lacks blinding for both participants and investigators. As a result bias will be introduced. Outcome assessments were, however, reviewed by investigators who were independent of those managing the study and blinded to treatment. Assessments were performed according to pre-defined criteria from the National Cancer Institute Working Group on CLL. .

- Maximum follow up was approximately five years. It should be noted that median survival is two to seven years in the population of interest. Therefore, a longer follow up would increase validity.

- The evidence base for the policy question of interest comprises of only one RCT.

- Quality of life data was only collected during the treatment period and is therefore inadequate to capture the long term effects of bendamustine or chlorambucil.

- Patients who discontinued therapy were not followed up, introducing the possibility of attrition bias.

- The ERG disagrees with the assumption in the economic evaluation that patients in PD have a blood transfusion every three weeks. Instead, the ERG believes a more appropriate assumption is that patients receive a blood transfusion every four weeks for the last six months of life, in both treatment arms. Under this revised assumption, the base case ICER falls from £12,000 to £7,000 per QALY.

- The ERG believes that the modelled treatment effect in terms of the hazard ratio for overall survival is too high. The submitted model uses a hazard ratio of 1.66, whereas the latest data indicates a hazard ratio of 1.3. In this case, Napp's base case ICER decreases from £12,000 to £11,700 per QALY. Using the updated

hazard ratio increases the ICER calculated by the ERG using a different frequency of blood transfusion from £7,000 to £9,700 per QALY.

- The ERG disagrees with the assumptions regarding dose intensities for bendamustine and chlorambucil and assumed frequencies of visits to a haematologist when not treated. However, these parameters affect the ICER to a lesser extent. Updating the assumption for dose intensities, Napp's base case ICER decreases from £12,000 to £11,600 per QALY. Updating the assumption for the frequency of visits to a haematologist when not treated, the ICER decreases from £12,000 to £11,500 per QALY.

1.4.3 Areas of uncertainty

- The ERG understands that there is variation in dosing schedules used for chlorambucil in UK practice and this may give rise to uncertainty in the economic evaluation. However, the ERG consider that the course of therapy used in Study 02CLLLIII is broadly consistent with UK clinical practice and that this therefore should be considered a relatively minor issue.

- Utility data to inform cost effectiveness modelling are sparse. This is an issue for all economic evaluations in this condition.

- Given that overall survival from the RCT is immature, Napp are forced to extrapolate survival over many years. Whilst their extrapolation is reasonable, we caution that this introduces uncertainty to the modelled overall survival, and hence to the cost-effectiveness of bendamustine.

- In the RCT, a higher proportion of patients in the chlorambucil arm were given second line drugs compared to patients in the bendamustine arm. The ERG is broadly satisfied with the submission's approach to incorporating second line drug costs, but has explored two alternative methods.

2   BACKGROUND

2.1   *Critique of manufacturer's description of underlying health problem*

A summary of the epidemiology, diagnosis, disease course, burden and quality of life associated with chronic lymphocytic leukaemia (CLL) is presented in Section 2.1 of the manufacturer's submission (Source: Napp Submission, Section 2.1, pp 18–21). Details on prognostic markers and staging are also included.

CLL is a B-cell lymphoproliferative disorder, in which the affected cells exhibit impaired apoptosis and prolonged lifespan, leading to their accumulation in the blood, bone marrow, liver spleen and lymph nodes (Source: Napp Submission, Section 2.1, pp18–21).

2.1.1   Epidemiology

The submission describes CLL as the most common leukaemia in industrialised countries. Incidence of CLL increases with age, currently accounting for 40% of leukaemia cases in people aged over 65 years (Source: Napp Submission, Section 2.1, pp 18–21). The submission reports incidence of 2.8 per 100,000 during 2007 in the UK with diagnosis of 2,339 new cases, based on data generated by Cancer Research UK (Source: Napp Submission, Section 2.1, pp 18–21).[4] However, other estimates exist. For example, based on ONS data, NICE suggest a rate of 3.9 per 100,000.[5] Smith and colleagues report incidence of 5.9 per 100,000 for years 2004–2009 in the UK, with a median age at diagnosis of 71 years. This is slightly older than the value reported in the submission of between 65 and 70 years (Source: Napp Submission, Section 2.1, pp18–21). It is clear that estimation of the population size is challenging; however, these variations may have implications for the assessment of cost effectiveness.

2.1.2   Diagnosis

Initially, patients may present with swollen lymph glands, anaemia, bruising or bleeding, although diagnosis may follow incidental asymptomatic identification of lymphocytosis. There may be thrombocytopenia, bacterial infections and splenomegaly and/or

hepatomegaly. However, most cases are diagnosed following a routine blood test. The submission also notes that for a definitive diagnosis to be given an absolute B-lymphocyte count of >5 × 109/L is required. In addition, the ERG note that this criterion applies when there is no extramedullary lymphoid tissue involvement. Further information is given with regard to immunophenotyping (Source: Napp Submission, Section 2.1, pp 18–21).

2.1.3   Prognosis

The Binet staging system[6] (Table 1) is identified in the submission as a tool frequently used in Europe to determine prognosis and appropriate therapy, whereas the Rai system is used more commonly in the United States (Source: Napp Submission, Section 2.1, pp 19).

Table 1. Binet staging system[6]

Stage	Organ enlargement*	Haemoglobin (g/dL)	Platelets (×10^9/L)
A	<3 areas	–	–
B	3–5 areas	≥10	≥100
C	Not considered	<10	and/or <100

*One area = lymph nodes >1cm in neck, axillae, groin or spleen, or liver enlargement.

The Binet system is further clarified with general survival times for each stage as follows:

> *Patients with stage A disease generally survive for at least 10 years. For patients with stage B disease, the median survival time is 5 to 8 years, and for those with stage C disease, it is 1 to 3 years.([18] Cancer Research UK, 2010) (Source: Napp Submission, Section 2.1, p20).*

Details are given on both the identification and consequences of cellular level abnormalities (Source: Napp Submission, Section 2.1, Table 2.1, pp 19). Additional characteristics associated with unfavourable outcomes are listed, such as unmutated immunoglobulin heavy chain (IgV_H) gene, expression of ZAP-70 on B-cells, CD38 expression and raised lactate dehydrogenase levels (Source: Napp Submission, Section 2.1, pp 19).

2.1.4   Course of the disease

It is noted in the submission that although CLL is incurable for the majority of patients, approximately one third will be initially asymptomatic and not require treatment at diagnosis. However, for those who do need treatment, achieving maximal depth and length of remission are recognised as important goals (Source: Napp Submission, Section 2.1, pp 20).

The heterogeneity of patients requiring treatment is mentioned with dependence on assessment by clinician to select the most appropriate approach to treatment. Although clinical symptoms are not specifically discussed in the submission, end-stage characteristics such as bulky disease, recurrent infection and Richter's transformation are noted (Source: Napp Submission, Section 2.1, pp 20).

2.1.5   Burden and quality of life.

The impact of CLL on quality of life is briefly acknowledged in the submission as follows:

- impaired physical, role, cognitive and social functioning [7][8]

- more sleep disturbance [8]

- increased fatigue; nausea and vomiting; appetite loss and constipation [7][8]

- It is also noted that patients with CLL are highly susceptible to infections, some of which can have serious consequences and are of particular relevance to the people concerned in this study (Source: Napp Submission, Section 2.4, p22–23). However, no further information about the impact of infection on patient quality of life (QoL) is given.

The submission highlights a study by Else and colleagues[8] reporting that the effect on QoL is greatest for patients with Binet stage A-progressive disease experiencing stage B symptoms (Source: Napp Submission, Section 2.1, pp 20). Binet stage A-progressive was defined in the paper by at least one of the following: lymphocyte doubling time <12 months; a downward trend in haemoglobin and/or platelets; >50% increase in the size of the liver and/or spleen and/or lymph nodes, or appearance of these signs if not

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previously present; constitutional symptoms (B-symptoms) attributable to the disease; e.g. pyrexia, night sweats, weight loss.

More attention is given in the submission to evidence linking a complete remission (CR) with increased progression free survival (PFS) and subsequently improved QoL (Source: Napp Submission, Section 2.1, pp 20). The difference in utility between CR and progressive disease (PD) was reported as 0.23 in a study by Beusterien and colleagues.[9] This figure, which was applied in the health economic analysis is supported by a further two studies: (i) Hancock suggested a utility difference of 0.2 between progressed and progression-free health states; and, (ii) Ferguson and colleague established a utility difference of 0.237 between progressed and progression free health states following first line treatment using time trade-off from members of the public.[10] [11]

2.1.6 Rationale for bendamustine

In Section 2.1 (page 24) of the manufacturer's submission, the rationale for bendamustine is given as an alternative for fludarabine. According to the submission, approximately 50% of patients with CLL are unsuitable for fludarabine due to its toxicity profile. However, no further details are given on the estimation of this figure. The current preference for patients in this position is chlorambucil which is generally well tolerated; however, this submission maintains that chlorambucil has relatively poor efficacy in terms of depth of remission (Source: Napp Submission, Section 2.1, pp 20). It is worth noting that there appears to be some variation in the UK regarding chlorambucil dose.

2.2   *Critique of manufacturer's overview of current service provision*

With regard to the number of patients considered to be eligible for chlorambucil (of which 90% are assumed to be eligible for bendamustine), the submission arrives at a figure of 1,182 (Source: Napp Submission, Section 2.2, pp 21).

The ambiguity concerning an appropriate treatment pathway is highlighted in Section 2.4, p25 of the manufacturer's submission. The most recent guideline from the British Committee on Standards in Haematology (BCSH) was published in 2004 and is yet to be

superseded.[12] However, definitions of appropriate treatment according to patient characteristics remain vague (Source: Napp Submission, Section 2.2, p21).

Pages 25–26 of the Napp submission outline current treatment for CLL, including presentation of a treatment algorithm which indicates the anticipated place for bendamustine. This is reproduced in Figure 1 (Source: Napp Submission, Section 2.4, p23).

Figure 1. UK treatment pathway for CLL
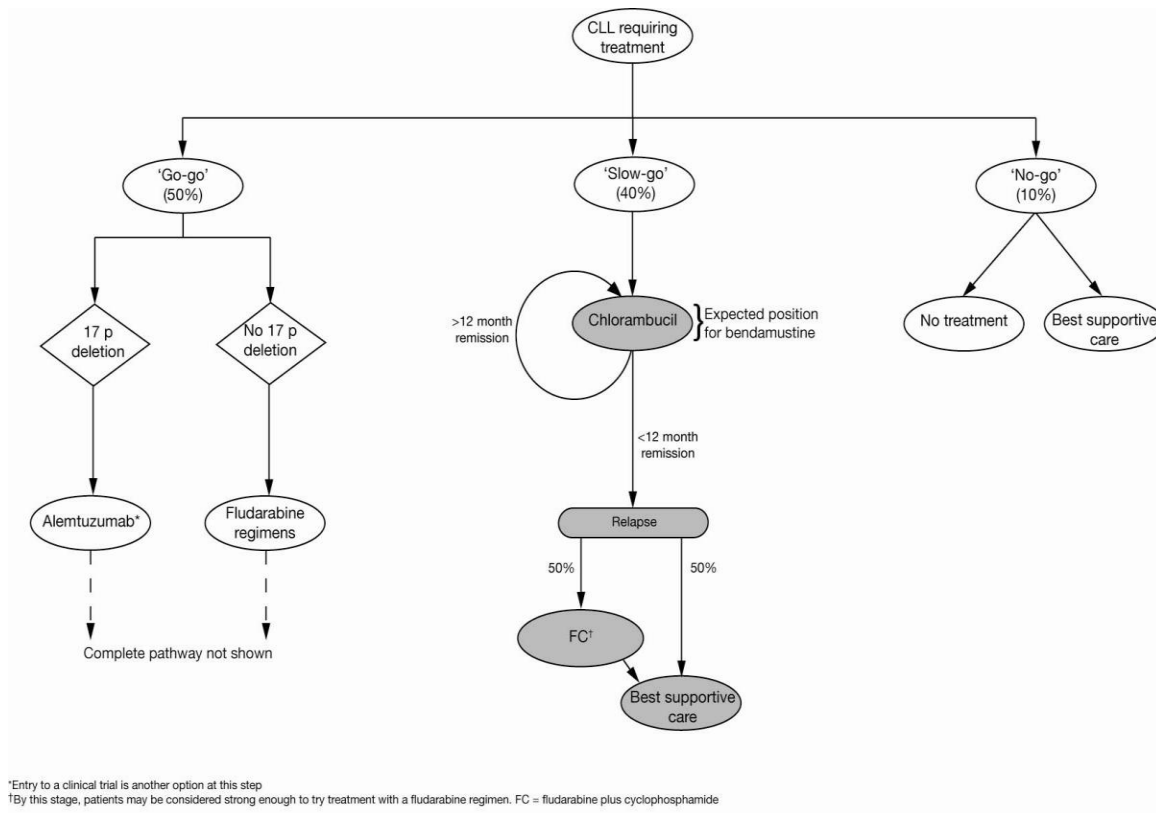
(Source: Napp Submission, Section 2.4, p23)

The pathway has been verified by UK CLL experts via a clinical advisory board commissioned by Napp.[13] It should be noted that although the pathway is relatively sophisticated as a description of treatment received, it remains insensitive to the fact that many patients progress to third and subsequent lines of treatment.

The submission highlights the inclusion of fludarabine in the treatment pathway, following first line therapy. This reflects the fact that a patient's condition may improve

following initial treatment to a point where they become suitable for fludarabine as a second line therapy (Source: Napp submission, Section 2.4, p23).

The lack of definitive criteria for determining which patients are 'unfit' for treatment with fludarabine combination therapy is discussed in Section 2.5 (page 23) of the Napp submission. As a result, the group of patients currently treated with chlorambucil in the UK is heterogeneous with regard to performance status, age and co-morbidities. The German CLL study group has developed the cumulative illness rating scales (CIRS) to provide an objective means of quantifying co-morbidities. According to the submission, it has been used to group patients into 'go-go', slow-go' and 'no-go' categories with respect to first line treatment, as displayed in Figure 1. However, although familiar to UK clinicians, this tool has not been validated and is not used routinely in UK practice. A trial planned in first line CLL has been designed to construct an objective 'real-life' definition of 'slow-go' or unsuitability for fludarabine combination therapy. Until then, decisions about first line treatment follow individual physician and patient judgments.

As the current standard, first line therapy in patients not considered suitable for fludarabine, chlorambucil is an appropriate comparator for the assessment of bendamustine in the UK.

The submission acknowledges the requirement of intravenous (IV) administration for bendamustine, requiring more clinical resources than oral chlorambucil (Source: Napp submission, Section 2.8–2.9, pp26). Although no novel infrastructure is required to support bendamustine administration, the impact of bendamustine adoption on the volume of patients requiring management of IV chemotherapy will vary among individual units depending on current demand from other conditions and capacity.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The population considered by the submission is:

> *Of those people who require therapy for CLL, approximately 50% will not be suitable for the 'gold standard' of fludarabine-containing regimens (usually because of their age or co-morbidities). In this submission, the population is limited to those untreated patients who are unsuitable for fludarabine-combination therapy. It is anticipated that this equates to 1,064 patients in England and Wales. (Source: Napp Submission, Section 4, p328)*

This is an adequate description of the population under consideration, and concurs with that defined in the NICE scope.[1] Overall, the ERG agree that the population considered is appropriate, but acknowledge the lack of definitive criteria for determining which patients are 'unfit' for treatment with fludarabine combination therapy (see Napp Submission, Section 2.5, Page 23–4).

3.2 Intervention

The intervention is bendamustine (Levact® i.v., Napp Pharmaceuticals Ltd).

The Committee for Human Medicinal Products (CHMP) issued a positive opinion on bendamustine on 18 March 2010. The European Commission (EC) formally accepted the decision on 7 July 2010 and the UK licence was granted by the Medicines and Healthcare Product Regulatory Agency (MHRA) on 3 August 2010. There is currently no European Public Assessment Report (EPAR) from the European Medicines Agency (EMEA). Bendamustine is licensed for:

> *First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate; indolent non-Hodgkin's lymphoma as monotherapy in patients who have progressed during, or within six months following treatment with rituximab or a rituximab containing regimen'; and front-line treatment of multiple myeloma (Durie-*

Salmon stage II with progress or stage III) in combination with prednisone in patients aged 65 years plus who are not eligible for auto-SCT and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment. (Source: Napp Submission, Section 1.4, p14)

Bendamustine is currently licensed in Germany under the trade name Ribomustin® for: first line therapy of advanced indolent non-Hodgkin lymphomas in a combination protocol; advanced multiple myeloma Stage II with progress or Stage III (according to the Durie–Salmon staging system[14]) in combination with prednisone; and, CLL. It is also licensed under the same trade name in Switzerland for chronic lymphocytic leukaemia. Bendamustine is licensed in the US under the trade name Treanda for: treatment of patients with chronic lymphocytic leukaemia; and, treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

There is no definitive treatment pathway for the treatment of CLL. Regional and national guidelines offer information on the various treatment options available but are not prescriptive. The manufacturer has defined the proposed treatment pathway (UK) based on these guidelines; verified by clinical advisors. Bendamustine is being considered for patients who are not suitable for fludarabine-based combination therapy.

3.3 Comparators

The single comparator was chlorambucil. The choice of comparator is in line with the final NICE scope. Chlorambucil is the current standard first line therapy for patients not suitable for a fludarabine-containing regimen. The Phase III study provides a direct comparison of bendamustine with chlorambucil.

3.4 Outcomes

There were two primary outcomes: overall response rate (ORR; included CR, nPR and PR). PFS; i.e. the time from randomisation to first PD or relapse after intercurrent remission or death owing to any cause (whichever occurred first). The response evaluation was based on the following criteria defined by the National Cancer Institute Sponsored Working Group on CLL. ([44, Cheson, Blood, 1996; 45,

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> *Cheson, Am J Hematol, 1988]) (Source: Napp Submission, Section 4, p28; and,*
> *Section 5.3.5, p41)*

Secondary endpoints included time to progression, duration of remission, and overall survival. Safety endpoints were infection rates and adverse events.

The outcomes are in line with those outlined in the final NICE scope[1] and are valid outcomes in oncology trials.[15] Response rate is generally considered clear evidence of antitumor activity and as such is an appropriate indicator of clinical benefit. The response criteria used in this trial are defined prospectively according to the National Cancer Institute Sponsored Working Group guidelines for CLL. The response criteria had to be met for at least eight weeks in order for patients to be classified as complete or partial responders. Patients were classified as 'non-responders', if neither PR nor CR were confirmed or their tumour response was not evaluable. A patient had stable disease if CR, PR, and PD criteria were not met. Response was assessed after three treatment cycles and at the end of treatment. The validation of response by an independent review committee blinded to treatment assignment adds further credibility to the study results and mitigates, to some extent, the lack of blinding in the study.[15]

The cost effectiveness of bendamustine is expressed as the cost to achieve an additional quality-adjusted life year (QALY) from treatment (Section 5).

3.5   Time frame

The time horizon used for the economic evaluation was 35 years.

> *NICE guidelines specify a lifetime analysis. By year 35 0.54% of the bendamustine*
> *group and 0.02% of the chlorambucil group are predicted to be alive by the model*
> *(Source: Napp Submission, Section 6.2.6, Page 81).*

The ERG agree that this is an appropriate timeframe.

3.6   Other relevant factors

No other relevant factors were identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

4.1.1.1 RCTs

Manufacturer searches were performed in the following databases on 22nd April, 2010:

- Ovid EMBASE

- Ovid MEDLINE®

- Ovid MEDLINE® In-Process & Other Non-Indexed Citations

- The COCHRANE Central Register of Controlled Trials (CENTRAL)

Separate search strategies were provided for EMBASE, Medline®, Medline® In-Process and CENTRAL by the manufacturer. EMBASE, Medline, Medline in-process database searches are based on a conjunction of terms identifying the CLL population and terms identifying bendamustine as an intervention. For each term, a combination of thesaurus headings (where possible) and free-text search-words was used. No outcomes were specified to limit the searches in any of these databases.

The EMBASE, Medline and Medline in-process searches included a study design filter to limit hits to clinical trials, meta-analysis and reviews. Cochrane searches did not include any study design filters. No additional filters were applied in any databases.

The combination of terms within the search strategies to define the CLL population and/or the intervention were appropriate and were replicable; however, in some cases there were significant discrepancies in the resulting hits which could have been accounted for given the search date and database/interface used. The ERG re-ran the base search strategy and checked for any additional results between April and September 2010; and, no additional RCTs were found. The ERG checked for ongoing

trials in the Meta Register of Controlled Trials and in the ClinicalTrials.gov online database, and no additional trials were found.

4.1.1.2 Non-RCTs

Manufacturer searches were performed in the following databases on 2nd July, 2010:

- Dialog EMBASE

- Dialog MEDLINE®

- Dialog MEDLINE® In-Process & Other Non-Indexed Citations

- The COCHRANE Central Register of Controlled Trials (CENTRAL)

- BIOSYS

Separate search strategies were provided for EMBASE, Medline®, Medline® In-Process, BIOSYS and CENTRAL by the manufacturer. EMBASE, Medline, Medline in-process database searches are based on a conjunction of terms identifying the CLL population and terms identifying bendamustine as an intervention. For each term, a combination of thesaurus headings (where possible) and free-text search-words was used. For CENTRAL searches only the CLL population was sought. No outcomes were specified to limit the searches in any of these databases.

The search strategy used for RCTs was extended to include non-RCTs (i.e. terms seeking studies that were prospective, retrospective, single-arm, observational, and cohort and case series). The base search strategy used in Medline® and Medline® In-Process was exactly replicated in EMBASE without translation of thesaurus headings. Consequently some of the search terms were not recognised; e.g. 'LEUKEMIA-LYMPHOCYTIC-CHRONIC-B-CELL.DE.' retrieved 0 results whereas applying the correct Emtree thesaurus term 'chronic lymphatic leukemia' retrieved 14,667 results. The manufacturer had also run key word searches which compensate for this discrepancy. The ERG note that this is not good practice; however, after re-running the searches using the correct thesaurus terms it was not considered problematic in the context of this submission.

The ERG re-ran the base search strategy and noted, in some cases, significant discrepancies in the resulting hits which could have been accounted for given the search date and database/interface used. The ERG checked for any additional results included in databases during August and September. This highlighted one paper which was not considered in the assessment although it was not considered that it would alter the discussion in the main submission: Pinilla-Ibarz J. McQuary A., Chronic lymphocytic leukemia: putting new treatment options into perspective. [Review]. *Cancer Control.* 2010;17(2 Suppl):4-15.

4.1.2 Databases and other sources including unpublished sources, any restrictions.

The following databases were searched: Ovid Embase, Ovid Medline[®], Ovid Medline[®] In-Process and other non-indexed citations, Cochrane Central. In addition the manufacturer also searched Biosys to identify non-RCTs.

Searches were not carried out in any other sources.

4.1.3 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The submission included RCTs which compared bendamustine with any other treatment for the treatment of CLL without specification of outcomes. Reports of studies not available in English were excluded.

The ERG considers that these inclusion and exclusion criteria are appropriate. However, the submission does not explain the process used in study selection (e.g. how many people were involved in reviewing abstracts and titles? How were differences in opinion resolved? What was the process of selection or rejection of retrieved papers?). These omissions theoretically limit the validity of the systematic review carried out to support the manufacturer submission.

4.1.4 Table of identified studies. What studies were included in the submission and what were excluded?

4.1.4.1 Relevant RCTs

The search results presented by the manufacturer identified 144 studies, of which one RCT in the relevant population, using the chosen comparator (chlorambucil) was identified: Study 02CLLIII (Table 2).

Table 2. List of relevant RCTs

Trial number	Intervention	Comparator	Population	Primary study ref
02CLLIII	Bendamustine	Chlorambucil	Previously untreated CLL	*Knauf WU, et al, J Clin Oncol* 2009;27:4378–4384

(Source: Napp Submission, Section 5.2.4, Page 34)

The submission reports data from Study 02CLLIII and references the clinical trial report, the published paper (Knauf *et al*) and a poster presentation at the 2009 American Society for Haematology (ASH) annual meeting (Knauf *et al*. Bendamustine in the treatment of chronic lymphocytic leukaemia – consistent superiority over chlorambucil in elderly patients and across clinically defined risk groups. *Blood* (ASH Annual Meeting Abstracts) 2009;**114**(22):abstract 2367).

The submission did not report which studies were excluded but gives reasons for exclusion in the QUOROM flowchart (see Napp Submission, Figure 5.1, p33). The reasons cited for exclusion are reasonable and in line with the search strategy.

4.1.4.2 Relevant non-RCTs

A systematic search of non-RCT evidence identified two studies (Table 3).

Table 3. List of relevant non-RCTs

Trial number	Intervention	Population	Objectives	Primary study ref
CLL2M	Bendamustine plus rituximab	Previously untreated CLL	To assess the efficacy and toxicity of bendamustine in combination with rituximab in previously untreated CLL patients	Fischer K, *et al. Blood* (ASH Annual Meeting Abstracts 2009;114:205
N/A	Bendamustine	Previously untreated and treated CLL		Kath R, *et al. J Cancer Res Clin Oncol* 2001;127:48–54

(Source: Napp Submission, Section 5.2.7, Page 34

Both studies were excluded from further discussion. In Fischer and colleagues follow-up is ongoing, with only interim results are available; and in Kath and colleagues the dose of bendamustine used in the trial did not reflect the licensed dosing of bendamustine or current clinical practice; and, only 13 patients in the study had previously untreated CLL. These were considered valid reasons for exclusion.

4.1.5 Details of any relevant studies that were not included in the submission?

One study was found that was not included in the submission: Pinilla-Ibarz J., McQuary A., Chronic lymphocytic leukemia: putting new treatment options into perspective. [Review]. *Cancer Control.* 2010;**17**(2 Suppl):4-15. This was not considered relevant to the submission.

4.1.6 Description and critique of manufacturers approach to validity assessment

The manufacturer reports the quality assessment of Study 02CLLIII according to the Centre for Reviews and Dissemination (CRD) assessment criteria for risk of bias in RCTs. Details of the critical appraisal carried out for the submission are shown alongside the ERG's critique in Table 4. Please note that italicised text has been cited directly from the submission (cross references are given).

Table 4. Critical appraisal of Study 02CLLIII

Critical appraisal criterion	*Napp assessment*	ERG comment
Study design	*Open label RCT*	This is an open-label study and therefore lacks blinding for both participants and investigators. However, outcomes were reviewed by an independent review team. *[The study] was a Phase III, open-label, multicentre parallel group international study comparing initial treatment of patients with CLL in Binet stage B or C requiring treatment. Patients were randomised to receive either intravenous bendamustine or oral chlorambucil (stratified by centre and Binet stage) (Source: Napp Submission, Section 5.3.2, p35–36).*
Were selection criteria adequately reported?	*Yes – (Source: Napp Submission, Section 5.3.3, pp38–39)*	Yes, the study eligibility criteria are specified and match those outlined in the final scope. To be eligible patients were required to; • *be treatment-naïve, legally competent adults ≤75 years of age,* • *have a WHO Performance Status of 0–2* • *have a life expectancy >3 months* • *have confirmed chronic B-cell lymphocytic leukaemia (co-expression of CD5, CD23 and either CD19 or CD20 or both)* • *have symptomatic Binet Stage B or C disease (Source: Napp Submission, Section 5.3.3, p38).* *In addition patients had to meet at least one of the following need-to-treat criteria;* • *haematopoietic insufficiency with non-haemolysis-induced haemoglobin ,10g/dl,* • *thrombocytopenia $<100 \times 10^{9}$/L (equivalent to Binet Stage C)* • *B symptoms* • *rapidly progressive disease* • *risk of organ complications from bulky lymphomas (Source: Napp Submission, Section 5.3.3, p39).* Patients with concomitant diseases were excluded from the study. This is standard practice in trials in oncology.

Were participants included in the study reflective of patients likely to receive the intervention in UK clinical practice?	*Yes – Study 02CLLIII compares bendamustine directly with chlorambucil in patients with previously untreated CLL who are not suitable for fludarabine-based therapy (Source: Napp Submission, Section 5.2.5, p34)*	Patients unsuitable for fludarabine are noted in the manufacturer's submission to be: *More elderly with co-morbidities and lower performance status (Source: Napp Submission, Section 2.1, p21).* Therefore the 65–70% of patients in this study with a WHO performance status of 0, coupled with a relatively young mean age of 63–64, may not be wholly representative of the target population (Source: Napp Submission, Section 5.3.4, Table 5.4, p40).
Was the study conducted in the UK (or were one or more centres of the multinational study located in the UK)?	*Yes – the study was carried out at 45 sites across Europe, including one centre in the UK (Source: Napp Submission, Section 5.3.2, p35)*	Study 02CLLIII was an international study, employing 45 centres across Europe, one of which was in the UK. No further details are reported regarding other sites involved or number of patients recruited in the UK. In addition, no analysis by country was performed. Since with any multicentre trial there may be inherent variations in disease management, knowing the proportion of trial participants based in the UK may improve confidence regarding applicability of trial results in this country.
How does the dosage regimen used in the study compare with that detailed in the Summary of Product Characteristics (SmPC)?	*As monotherapy for first line treatment of CLL: 100 mg/m^2 body surface area on Days 1 and 2, every four weeks.(Source: Napp Submission, Section 1.10, Table 1.1, p16)*	The dosage regimen used for bendamustine is the same as the dosage regimen proposed in the Summary of Product Characteristics (SmPC) and is in accordance with the license. However, as already noted, the dosage regimen for chlorambucil is subject to variation in clinical practice – see Section 2 of the ERG report for further details.
Was a justification for the sample size provided?	*Yes – (Source: Napp Submission, Section 5.3.6, pp43–45)*	*Sample size calculations were based on results from a study comparing fludarabine and chlorambucil in previously untreated patients [16] that suggested a 30% difference in ORR between treatments and a 6-month difference in PFS. From this it was calculated that approximately 42 patients would be needed in each group to achieve 80% power to show a significant difference in ORR at the 0.05 significance level (Source: Napp Submission, Section 5.3.6, p44).* For the total bendamustine population of 148, the ORR was 50% i.e. greater than was anticipated (Source: Napp Submission, Section 6.3.1,Table 6.2,

		p84).
		With regard to PFS, according to a previous study, the sample size required was calculated as 326 patients in total.[16] However, due to uncertainties regarding assumptions in the previous study, a five-stage adaptive group sequential procedure was used, which gave an estimated required sample size of 350 people (Source: Napp Submission, Section 5.3.6, p44–45).
What randomisation technique was used?	*Patients were randomised 1:1 to receive either bendamustine or chlorambucil according to a computer-generated randomisation list. They were randomised consecutively in the order of study entry. Randomisation was in blocks of four (investigators were unaware of this) and was prospectively stratified by study centre and Binet stage. (Source: Napp Submission, Section 5.3.2, p37)*	This is an acceptable system of randomisation.
Were patients recruited prospectively?	*Yes – (Source: Napp Submission, Section 5.3.2, p37)*	Yes, patients were recruited prospectively.
Were patients recruited consecutively?	*Not reported – (Source: Napp Submission, Section 5.3.2, pp35–39)*	Unclear. The submission states that participants were randomised consecutively in the order of study entry, not that they were recruited consecutively (Source: Napp Submission, Section 5.3.2, p37). Therefore it is not known if all people matching the stated inclusion criteria were enrolled into the study.
Were the individuals undertaking the outcomes assessment aware of allocation?	*Yes – the study was open-label. A blinded study was not appropriate given the different methods of administration of bendamustine (i.v. infusion) and chlormabucil (oral). (Source: Napp Submission, Section 9.3.1, p174)*	Due to the different routes of administration for the intervention and comparator, blinding was not performed. It is unclear whether it would have been feasible to blind the participants and investigators, but it should be noted that awareness of allocation will have introduced the potential for bias in the study. The investigators' assessments were, however, reviewed by an independent committee for response

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	However, the investigators' assessments of patients' responses were checked by an independent committee for response assessment (ICRA); members of the ICRA were blinded to treatment. (Source: Napp Submission, Section 5.3.2, p37)	assessment (ICRA). All results quoted in the manufacturer's submission were assessed by the ICRA (Source: Napp Submission, Section 5.3.2, p37). The submission notes some discrepancies between investigators and reviewers. For example, the investigators assessments gave an ORR of 40%, but following an independent assessment, this was adjusted to 31% (Source: Napp Submission, Section 5.10.4, p67). The procedure for disagreement between results is not reported. It is also unclear whether individual ICRA members were blinded to the findings of other ICRA members. Although a definition for progression is given in the submission and the trial report there is no confirmation of independent assessment of progression. The ERG assume that assessment of progression was done by the Investigators who were not blinded to treatment thus increasing the likelihood for bias.
Was follow-up adequate and was loss to follow-up reported or explained?	*Yes – Subjects were followed up every three months. The follow-up period ended one year after the last enrolled patient completed treatment. (Source: Napp Submission, Section 5.3.2, p37)* *Loss to follow-up was reported as only one in the chlorambucil arm and none in the bendamustine arm.(Source: Napp Submission, Section 5.3.8, Figure 5.3, p47)*	The minimum follow up period was 12 months, with interim analyses carried out quarterly. However, as recruitment took place over four years, and the follow-up period ended one year after the last enrolled patient, some subjects were monitored for approximately five years in total. It should be noted that median survival is two to seven years in the population of interest. Therefore, a longer follow up has been advocated for CLL; for example, a study reported in *Oncology Times* showed changes in overall survival rates after six years.

Were the statistical analyses used appropriate?	*Statistical analysis of the two primary endpoints was by a combination of a priori sequenced hypothesis testing and an adaptive group sequential test procedure. All tests were two-tailed, using a multiple significance level of α = 5%. ORR was analysed by Fisher's exact test, and PFS by a log-rank test* *The secondary efficacy endpoints (TTP, duration of remission, duration of CR and duration of PR) were analysed using the log-rank test, stratified for Binet stage. (Source: Napp Submission, Section 5.5, pp48–55)*	The approach to the statistical analysis of Study 02CLLIII study is considered appropriate – see Section 4.1.9 of the ERG report for further detail
Were appropriate measures of variability reported?	*Yes. (Source: Napp Submission, Section 5.5, pp48–55)*	95% CIs and/or P values are available for most outcomes reported.
Was an intention-to –treat analysis undertaken?	*Yes – the efficacy analyses were carried out on the ITT population. (Source: Napp Submission, Section 9.3.1, p174)*	Yes, the analysis adopts 'intention to treat' principles.
Were there any confounding factors that may attenuate the interpretation of the results of the study?	*None reported. (Source: Napp Submission, Section 9.3.1, pp174–175)*	Patients were randomised on study entry and both groups have similar baseline characteristics. Reasons are given for patients who did not complete the study, and the numbers of these are comparable between arms (Source: Napp submission, Section 5.3.8, Figure 5.3, p47). However, lack of blinding may have introduced some bias.
Did the study report data for relevant prognostic factors?	*Yes – (Source: Napp Submission, Section 5.5 pp48–55)*	The relevant prognostic factors are quoted in the manufacturer's submission as follows: *A post-hoc analysis was carried out to compare the efficacy and tolerability of bendamustine and chlorambucil in subgroups of patients defined by age (<65 years vs. ≥65 years) and specific indicators of disease activity*

		(presence of B-symptoms, Binet stage and lactate dehydrogenase levels). These factors are of interest because each can influence prognosis (Source: Napp Submission, Section 5.3.7, p46).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*Yes – quality of life was measured during the study. It is not reported in the published paper, but is fully documented in the study report. (Source: Napp Submission, Section 9.3.1, p174)*	Although no numerical values are given, the submission notes: *Patients' overall quality of life was modestly improved in both groups during treatment with no significant differences between the groups. Significant differences in favour of chlorambucil were seen in the following individual parameters:physical functioning, role functioning, emotional functioning, fatigue and appetite loss. The quality of life data collected during the trial reflected the scenario in which patients receiving a more effective therapy (bendamustine) experienced a greater number of adverse events during the treatment period leading to a quality of life detriment in some health dimensions. The quality of life data collected in the trial were not appropriate to capture the long-term benefit of bendamustine after therapy was stopped, because they were only collected during the treatment period and patients who were discontinued from the study were not followed up with respect to quality of life. (Napp Submission, Section 5.5, p54).*

4.1.7 Description and critique of manufacturers outcome selection

There were two primary outcomes: ORR (which included CR, nPR and PR) and PFS. Assessments of responses were based on criteria defined by the National Cancer Institute Sponsored Working Group on CLL, and had to be met for at least eight weeks. [2] [3] After the last treatment cycle, patients were monitored for response and survival at three-month intervals. Final assessment of response was assessed by an Independent Committee for Response Assessment (ICRA) and classified as CR, nPR, PR, stable disease (SD), or progressive disease (PD) based on the National Cancer Institute Sponsored Working Group criteria.[2][3] PFS is defined as the time from randomisation to first PD or relapse after inter-current remission or death for any cause.

Secondary outcome measures included time to progression (TTP), duration of response/remission, OS, QoL and Aes. TTP is defined as the time from randomisation to first PD or relapse after inter-current remission of CLL-related death. Duration of

response/remission is the time from maximum therapeutic response (CR, nPR, PR) to PD or death for any cause.

The outcome measures concur with those specified in the final scope issued by NICE. Response rate is generally considered clear evidence of antitumor activity and a surrogate for clinical benefit. The response criteria used are defined prospectively and applied appropriately.

In order to minimise the risk of bias associated with open-label studies, the assessment of progression was reviewed by three independent experts who were blinded to treatment assignment. The experts were required to consider tumour evaluations on all patients and agree on the best response and date of progression. A definition for progression is given in the submission and the clinical trial report...

4.1.8 Describe and critique the statistical approach used

4.1.8.1 Study 02CLL, Statistical Analysis: Primary endpoints

The final statistical analysis was a culmination of several interim tests.

> *Statistical analysis of the two primary endpoints was by a combination of a priori sequenced hypothesis testing and an adaptive group sequential test procedure. All tests were two tailed, using a multiple significance level of α = 5%. ORR was analysed by Fisher's exact test, and PFS by a log-rank test. Analysis of both endpoints was stratified to adjust for the influence of patients' status according to Binet stage (Binet B or Binet C). Relative risk and rate differences (and their associated 95% CIs) were calculated post hoc. (Source: Napp Submission, Section 5.3.6., p44).*

With regard to the *post hoc* calculations, we assume that the submission is referring to the final adjustment of the p-value to account for multiple testing.

4.1.8.2 Study 02CLL, Statistical Analysis: Interim analyses

Three interim analyses were performed prior to the main analysis of the final sample. This is a common technique for trials involving individuals at high risk of a negative outcome, since the results of the interim analysis may be used to stop the trial early if a

treatment appears harmful. However, because several tests were used there was more likely to be a significant result by chance alone. To account for this, the manufacturers lowered the threshold level to reject a type I error (p-value) to 0.016.

A five-stage adaptive group sequential procedure with Pocock cut-offs of αi = 0.016 was used. A maximum of four interim analyses was planned, of which three were performed (the first after 85 patients treated with a follow-up of at least 5 months, the second after 158 patients and the third after 264 patients). In each interim analysis, ORR was tested first; PFS was only tested if ORR was significant, thus controlling for multiple testing. (Source: Napp Submission, Section 5.3.6., p49).

The P values of the individual sequences were combined using the Φ–1 method; as the patients were still under observation, these were used only to determine whether to terminate the study or continue using the new sample size. At the third interim analysis the Independent Data Monitoring Committee recommended termination of recruitment and the final analysis be performed using the data available. (Source: Napp Submission, Section 5.3.6., p44).

4.1.8.3 Study 02CLL, Statistical Analysis: Secondary endpoints

The secondary efficacy endpoints (TTP, duration of remission, duration of CR and duration of PR) were analysed using the log-rank test, stratified for Binet stage. (Source: Napp Submission, Section 5.3.6., p44).

The safety analysis was descriptive and comprised all documented adverse events, serious adverse events, laboratory variables, and vital signs (blood pressure, pulse, temperature). (Source: Napp Submission, Section 5.3.6., p49).

Hazard ratios (and their associated 95% CIs) were calculated post hoc. (Source: Napp Submission, Section 5.3.6., p44).

4.1.8.4 Study 02CLL, Statistical Analysis: Sample size and power calculation

The adaptive design employed by the manufacturers (described below) is a valid technique using accumulated data in order to modify aspects of the study, such as

sample size reassessment. In this case, the sample sizes for ORR and PFS appear correct.

> *Sample size calculations were based on results from a study comparing fludarabine and chlorambucil in previously untreated patients that suggested a 30% difference in ORR between treatments and a 6-month difference in PFS. From this, it was calculated that approximately 42 patients would be needed in each group to achieve 80% power to show a significant difference in ORR at the 0.05 significance level. (Source: Napp Submission, Section 5.3.6.,p p44).*

> *The sample size required for PFS was calculated as 326 patients in total (if no interim analyses were to be performed). As it was uncertain whether the assumptions used in the previous study would hold also for this study, the five-stage adaptive group sequential procedure described above was used. Using this approach, the final sample size was estimated to be approximately 350 patients. (Source: Napp Submission, Section 5.3.6., pp44–45).*

With regard to missing data, patients with CLL-related death and non-CLL related deaths that occurred during remission were censored at the time of death. In addition;

> *Patients who were alive without progression at the time of the final analysis were right censored and entered into the analysis with time from start of treatment to the last date at which occurrence of PD or relapse could be excluded by tumour evaluation. (Source: Napp Submission, Section 5.3.6., p45)*

This is an acceptable method of utilising data up to the point of analysis.

Overall, following discussion with a statistical expert within the ERG's Institute, Obioha Ukoumunne, it is the opinion of the ERG that the data for this study have been analysed rigorously.

4.2   Summary statement

The submission contains all the relevant studies and the relevant data within those studies. The submitted evidence also adequately reflects the decision problem defined in the submission.

4.3 Summary of submitted evidence

4.3.1 Summary of results

4.3.1.1 Primary endpoint results

There were two primary endpoints: ORR and PFS.

Overall response rate

Study 02CLLIII adequately assesses response according to pre-defined criteria. Patients were assessed for response after three cycles of treatment. Two additional cycles were recommended for patients with CR or PR, up to a maximum limit of six cycles in total. The response criteria according to the National Cancer Institute Sponsored Working Group Guidelines for CLL had to be met for at least eight weeks. Patients with no change were allowed to receive additional cycles at the discretion of the investigator to the same maximum of six cycles. After the last treatment cycle patients were monitored for response and survival at three-month intervals. Final assessment of best response was performed, blind to treatment allocation, by an ICRA and classified as CR, PR or nPR, SD or PD based on the National Cancer Institute Working Group Criteria.

Overall, 110 bendamustine-treated patients (68%), and 48 (31%) chlorambucil-treated patients achieved a CR or PR (P<0.0001) (Figure 2). The proportion of patients with a CR was higher with bendamustine than with chlorambucil (31% vs 2%), as was the proportion with nPR (11% vs 3%). Patients with Stage C disease showed a higher likelihood of CR with bendamustine: nine patients (20%) with bendamustine showed a CR, whereas no chlorambucil patients did so.

Figure 2. Response rates
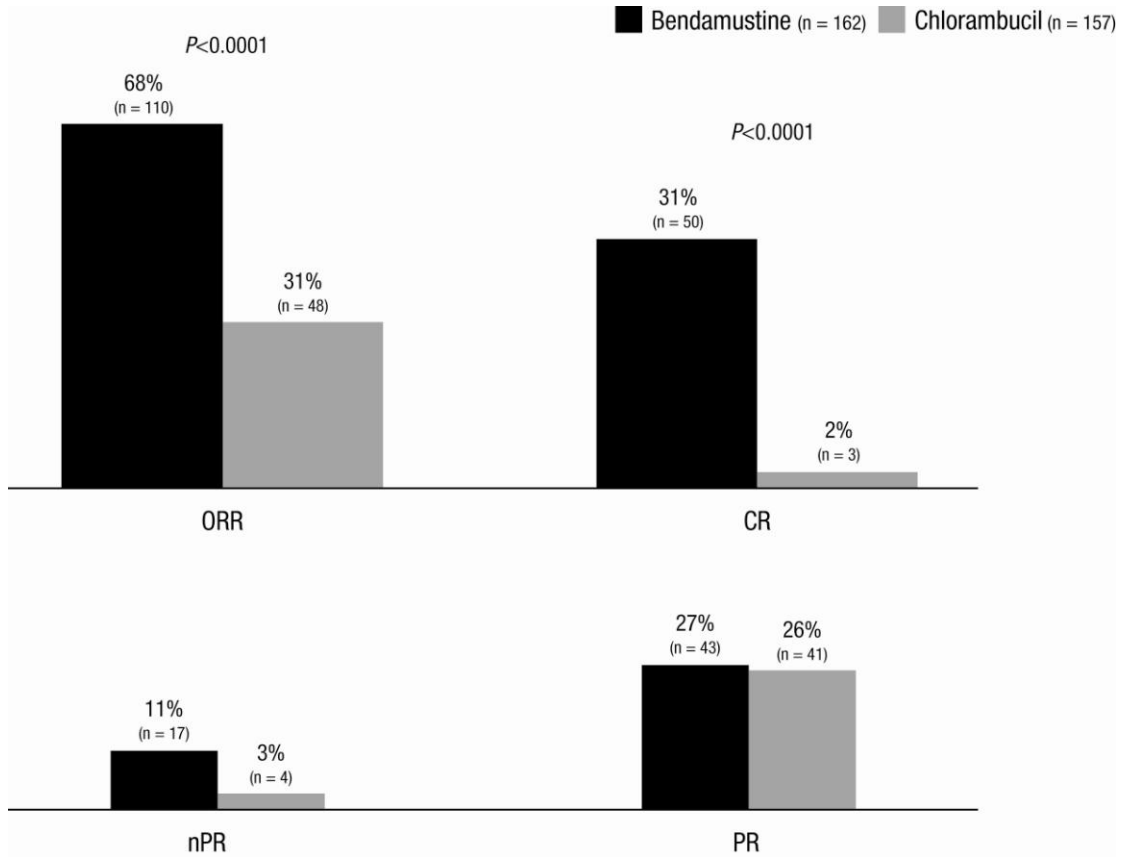
(Source: Napp submission, Section 5.5, Figure 5.4, Page 49)

Table 5 shows the response rates according to Binet stage. Regardless of Binet stage, patients showed a higher likelihood of CR with bendamustine than with chlorambucil.

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Table 5. Response rates according to Binet stage (ITT population)

| | Number (%) of patients | | Relative risk | Rate difference | P |
	Bendamustine	Chlorambucil	(95% CI)	(95% CI)	value
Binet B	**n=116**	**n=111**			
CR	41 (35.3)	3 (2.7)	13.08 (5.81–29.46)	0.326 (0.23–0.42)	0.0000
nPR	14 (12.1)	4 (3.6)	3.35 (1.22–9.16)	0.085 (0.02–0.15)	0.0186
PR	27 (23.3)	31 (27.9)	0.83 (1.30–0.53)	-0.047 (-0.16–0.07)	0.4228
ORR	82 (70.7)	38 (34.2)	2.06 (1.59–2.68)	0.365 (0.24–0.48)	0.0000
Binet C	**n=46**	**n=46**			
	9 (19.6)	0 0		0.196 (0.08–0.31)	0.0017
	3 (6.5)	0 0		0.065 (-0.01–0.14)	0.0799
	16 (34.8)	10 (21.7)	1.60 (0.82–3.12)	0.130 (-0.05–0.31)	0.1671
	28 (60.9)	10 (21.7)	2.80 (1.64–4.77)	0.391 (0.21–0.58)	0.0002
Binet B+C	**n=162**	**n=157**			
CR	50 (30.9)	3 (1.9)	16.15 (7.36–35.46)	0.290 (0.22–0.36)	0.0000
nPR	17 (10.5)	4 (2.5)	4.12 (1.56–10.88)	0.079 (0.03–0.13)	0.0043
PR	43 (26.5)	41 (26.1)	1.02 (0.70–1.47)	(-0.09–0.10)	0.9309
ORR	110 (67.9)	48 (30.6)	2.22 (1.76–2.81)	(0.27–0.48)	0.0000

(Source: Napp Submission, Section 5.5, Page 55)

Table 6 shows the response rates according to patient age. The data show similar response rates regardless of age between treatment groups: patients aged <65 years had an ORR of 72%, compared with 64% in patients aged >65 years (P>0.3). In the chlorambucil group, the corresponding figures were 28% and 33%, respectively (P>0.6). This provides some reassurance that age *per se* does not act as a determinant of response. This may be important for practice given that age along with co-morbidity or performance status may be a determinant of clinician judgment of suitability for fludarabine-based treatment.

Table 6. Response rates according to age (ITT population)

| | Number (%) of patients <65 years | | Number (%) of patients ≥65 years | |
	Bendamustine	Chlorambucil	Bendamustine	Chlorambucil
n	88	74	74	83
CR	31 (35)	2 (3)	19 (26)	1 (1)
nPR	12 (14)	1 (1)	5 (7)	3 (4)
PR	20 (23)	18 (24)	23 (31)	23 (28)
Unconfirmed response	2 (2)	3 (4)	2 (3)	2 (2)
SD	11 (13)	11 (15)	8 (11)	21 (25)
PD	7 (8)	28 (38)	8 (11)	25 (30)
Not examined	5 (6)	11 (15)	9 (12)	8 (10)
ORR	63 (72)	21 (28)	47 (64)	27 (33)

(Source: Napp Submission, Section 5.5, Table 5.6, Page 51)

<u>Progression-free survival</u>

Figure 3 shows PFS. Median PFS was significantly longer with bendamustine than with chlorambucil (21.6 months vs 8.3 months; P<0.0001). This difference was evident in patients with Binet stage B disease (21.4 months vs 9.0 months) as well as in Stage C disease (25.4 months vs 6.3 months). The manufacturer notes that patients in the bendamustine group with Stage C disease had a longer PFS than those with Stage B disease, whereas this was not the case in the chlorambucil group. However, there were only 46 patients with Stage C disease in each treatment arm which makes it difficult to assess whether this a chance finding, and this is acknowledged in the submission. Nine patients in the bendamustine group with stage C disease achieved CR, compared with none in the chlorambucil group. The results presented suggest that bendamustine offers an effective treatment option even for those patients with advanced disease.

Figure 3. PFS (ITT population)
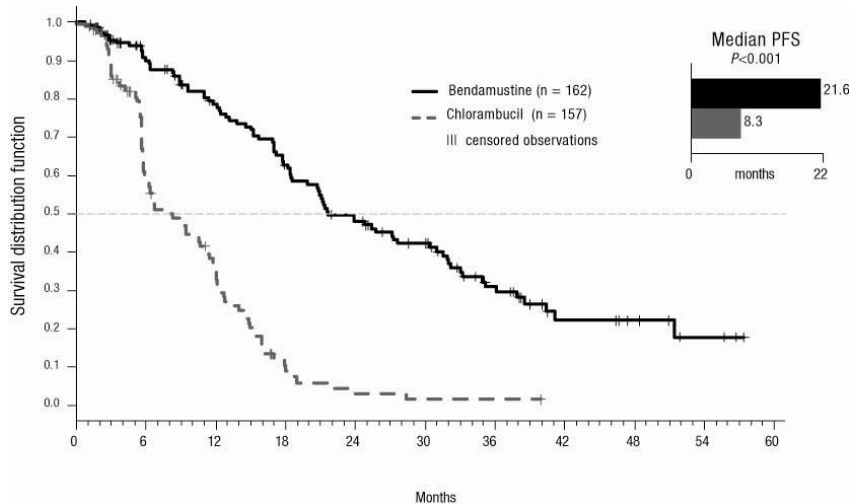
(Source: Napp Submission, Section 5.5, Page 52)

As seen for ORR, age had no impact on PFS, benefits being still apparent when comparing patients aged above and below 65 years. Likewise, this was also true of comparisons between patients with Binet Stage B or C disease: hazard ratios (95% Cis) were 4.13 (2.81–6.06) for patients with Stage B disease (P<0.0001) and 5.18 (2.66–10.07) for patients with Stage C disease (P<0.0001). The manufacturer also notes that patients in the bendamustine group who had B symptoms had a significantly longer median PFS than those without (30.4 months vs 17.7 months; P<0.0001). Median PFS was not affected by the presence of B symptoms in the chlorambucil group

PFS was significantly longer with bendamustine than with chlorambucil. Studies in other cancers prolonged PFS is assumed to be associated with improved quality of life and this is considered of clinical significance.[17]

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4.3.1.2 Secondary endpoint results: Duration of response

Figure 4 shows duration of response. According to the Independent Committee for Response Assessment (ICRA), there were 158 responders. The median duration of response was 21.8 months in the bendamustine group and 8.0 months in the chlorambucil group [hazard ratio (95% CI) = 4.46 (2.89–6.88); P<0.0001].

Figure 4. Duration of complete and partial response (ITT population)
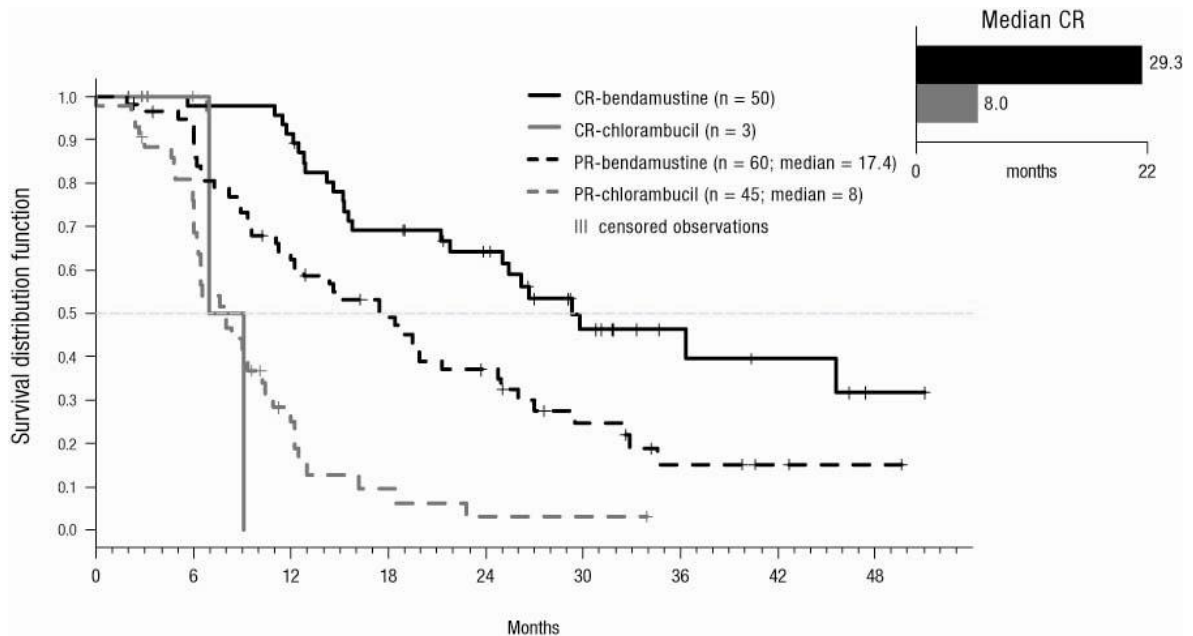
(Source: Napp Submission, Section 5.5, Figure 5.6, Page 53)

The median duration of CR was 29.3 months for patients treated with bendamustine and 8.0 months for those treated with chlorambucil [hazard ratio (95% CI) = 45.11 (3.87–525.3); P<0.0001]. The median duration of PR was 17.4 months with bendamustine and 8.0 months with chlorambucil [hazard ratio (95% CI)= 2.84 (1.77–4.56); P<0.0001].

4.3.1.3 Secondary endpoint results: Time to progression

Figure 5 shows time to progression (TTP) i.e. the time from the start of therapy to PD or relapse after intercurrent remission or death due to CLL. Median TTP was significantly longer for bendamustine than for chlorambucil [23.9 months vs 8.3 months; hazard ratio (95% CI) = 4.70 (3.36–6.58), P<0.0001.

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Figure **5**. TTP (ITT population)
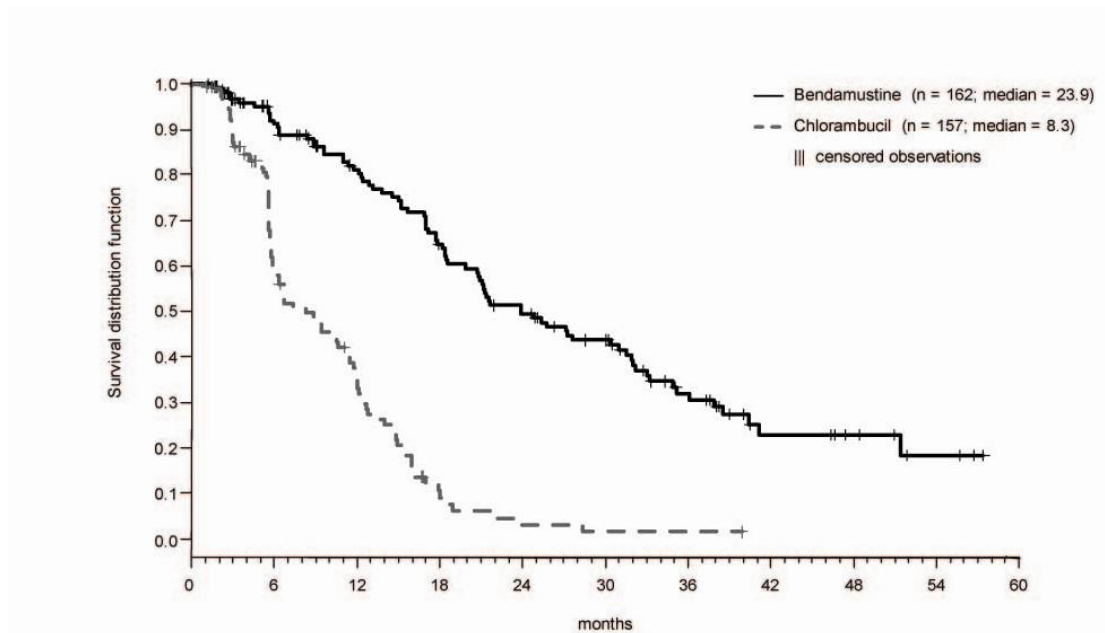
(Source: Napp submission, Section 5.5, Figure 5.7, Page 53)

4.3.1.4 Secondary endpoint results: Overall survival

The main submission reports the results of the 35-month survival analysis. These data suggest an OS advantage for bendamustine, but show no statistically significant survival benefit (P=0.1623). Overall, 72 patients (31 in the bendamustine group and 41 in the chlorambucil group) died during follow-up. Death due to CLL was reported for 13 patients in the bendamustine group and 21 patients in the chlorambucil group (65.4 monthsThe hazard ratio (95% CI) was 1.45 (0.91–2.31).

A breakdown of OS according to response shows that it appears to be the numbers of patients achieving CR and nPR that are driving the overall survival advantage (Figure 6). The submission cites published literature which contains increasing evidence that the depth of response among CLL patients, particularly CR, is a good indicator of whether an OS benefit is likely to be achieved.[16] [18-22]

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Figure **6**. Overall survival according to response (ITT population)

(Source: Napp Submission, Section 5.5, Figure 5.8, p54)

Recently available data (median observation time 54 months) confirm that bendamustine shows a statistically significant advantage in overall survival, and a much longer time to next treatment than chlorambucil. However, while this supports the analysis presented in the main submission 54 months is still a short period of time to measure OS.

4.3.1.5 Secondary endpoint results: Quality of life

Patients' QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life (QoL) questionnaire during the treatment period. Patients' overall QoL (measure by global health status) was modestly improved on both treatments with no significant differences between groups.

The largest relative differences were reported as seen for fatigue, nausea and vomiting, dyspnoea, and appetite loss; these were consistent with the higher incidence of these Aes in the bendamustine group but these impacts on specific domains do not appear to translate into a difference in impact on the global health status question.

The QoL data collected in the trial may reflect the scenario in which patients receiving an effective therapy experience a greater number of AEs during the treatment period leading to a QoL detriment in some health dimensions. In addition, QoL outcomes in an open-label study may be subject to measurement bias. The QoL data collected in the trial were not appropriate to capture the long-term benefit of bendamustine after therapy

was stopped, having only been collected during the treatment period (i.e. for a maximum of six cycles). Unfortunately, patients who discontinued the study were not followed up with respect to QoL.

The EORTC-C30 data were mapped to obtain utility scores (which were applied in the economic model during the treatment period) and to inform a baseline utility score when applying the utility values from Beusterien and colleagues after the treatment period. This method of estimating is in line with previous STA reports for new interventions in this therapy area.

4.3.1.6 Safety

Study 02CLLIII informed the safety analysis. The safety population (patients who received at least one dose of study medication) included 312 patients (161 in the bendamustine group and 151 in the chlorambucil group. Overall, adverse events (Aes) were reported in 143 patients (89%) in the bendamustine group and 122 (81%) in the chlorambucil group. A total of 23 patients – 18 from the bendamustine and five from the chlorambucil group – were withdrawn from the study due to unacceptable toxicity or the risk/benefit assessment was no longer acceptable.[23 24] One hundred and thirty-four patients (83%) in the bendamustine group and 99 (66%) in the chlorambucil group had adverse events that were considered to be related to treatment. There were 72 deaths during the study: 31 in the bendamustine group and 41 in the chlorambucil group. Most occurred at least 100 days after the last dose of the study drug; disease progression was the most common cause of death.

The most frequent AEs leading to termination of the study were hypersensitivity reactions affecting skin and subcutaneous tissue (nine patients treated with bendamustine, two treated with chlorambucil).[23 24] Two patients in the bendamustine arm but none in the chlorambucil arm experienced Grade 3 hypersensitivity reactions. Grade 4 hypersensitivity was not observed at all.[23 24] AE s were reported in 143 (89%) of 161 patients in the bendamustine group and 122 (81%) of 151 in the chlorambucil group. The most frequently occurring AEs were haematological with the number of events being higher in the bendamustine arm (neutropaenia in 27%, thrombocytopenia in 25%, and anaemia in 22% of patients) than in the chlorambucil arm (neutropaenia in 14%, thrombocytopenia in 21%, and anaemia in 14% of patients).[23 24]. Neutropaenia of

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National Cancer Institute Working Group Grade 3 or 4 occurred in 37 bendamustine-treated patients (23%) and 16 chlorambucil-treated patients (11%), and granulocyte colony-stimulating factors (GCSFs) were used at the discretion of the investigators in 23 (3%) of 783 cycles in the bendamustine and in two (0.3%) of 733 cycles in the chlorambucil arm.[23][24] Erythropoetin was used in 0.5% and 0.3% of all cycles in the bendamustine and chlorambucil arms, respectively.[23][24]

Adherence to the dosing schedule was high in both treatment arms. In total, 90% of the planned bendamustine dose and 95% of the planned chlorambucil dose were administered.[23][24]

Infections of Grade 3 or 4 severity occurred in 8% and 3% of patients in the bendamustine and chlorambucil arm respectively. There was one Grade 4 infection in the chlorambucil arm.[24]

Gastrointestinal events (nausea, vomiting, and diarrhoea) were more frequent with bendamustine than with chlorambucil.[23][24] Fifty-eight patients (36%) in the bendamustine group and six patients (4%) in the chlorambucil group received antiemetic therapy.[24] Antiemetics were given as preventive therapy in 46 of the 58 patients in the bendamustine group and in two of six patients in the chlorambucil group.[23][24]

There was a single report of a new malignancy during follow-up; a bronchial carcinoma, in a patient who had received bendamustine, was detected 12 months after the treatment with bendamustine was finished.[23][24]

There were two reports on tumor lysis syndrome, both in patients following the first cycle of bendamustine. However, these events were not fatal and the two patients continued treatment.[23][24]

During the study there were nine documented, treatment-related hospitalisations in the bendamustine group and three in the chlorambucil group. One patient (<1%) in the bendamustine group died during the treatment period (owing to COPD and acute cardiac and pulmonary failure), compared with three patients (2%) in the chlorambucil group (owing to CLL, haemorrhagia and heart failure). These death rates are comparable with that in a recent study of FCR vs FC ([9] Hallek, Blood 2009), in which treatment-related

death was reported for 2% of patients treated with FCR and 1.5% treated with FC. (Source: Napp Submission, Section 5.9.2, page 63)

The AE profile reported is consistent with that expected in this patient population.

4.3.2 Critique of submitted evidence syntheses

No meta-analysis was required. The effectiveness summary in the manufacturer submission reports the results as obtained in the Phase III clinical trial.

4.3.3 Summary of clinical effectiveness

The submission contains all relevant studies and the relevant data within those studies. One additional paper was found, a review paper reporting treatment options for CLL which was not considered relevant to the submission. The submitted evidence also adequately reflects the decision problem defined in the submission.

The submission includes one clinical study: bendamustine hydrochloride versus chlorambucil in treatment-naïve patients (with Binet stage B/C) B-CLL requiring therapy. This was a Phase III, randomised, open-label, multicentre trial of 319 participants. 162 patients were randomised to bendamustine, and 157 patients were randomised to chlorambucil.

In summary the benefits identified for bendamustine are as follows:

- Patients receiving bendamustine had a higher ORR than those in the chlorambucil group (68% vs 31%; P<0.0001). The median PFS was also significantly longer with bendamustine than with chlorambucil (21.6 months vs 8.3 months; P<0.0001).

- The results for OS showed an improvement in the number of events between the two treatments with 31 deaths reported in the bendamustine group and 41 in the chlorambucil group [HR 1.45; 95% CI 0.91–2.31]. However, no statistically significant treatment difference in OS at the time of the main analysis. Results from an updated trial analyses (median observation time 54 months) confirm that bendamustine offers significantly greater response rates and PFS, and a much longer time to next treatment than chlorambucil.

- Adverse events were reported in 89% of patients in the bendamustine group and 81% of the chlorambucil group, with the most common being haematologic in nature. Severe infections of Grade 3 or 4 occurred in 8% and 3% of treated patients in the bendamustine and chlorambucil arm, respectively, with one singular Grade 4 infection in the chlorambucil arm. In general, these events are consistent with those expected in this patient population.

5 ECONOMIC EVALUATION

In this section, the cost-effectiveness analysis included in the submission is assessed. Overall, the model and report are of good quality. The approach is reasonable and no logical errors in the economic model were identified. However, the ERG disagrees with the following assumptions, which have consequences for the estimated cost-effectiveness of bendamustine:

- Timings of blood transfusions

- OS benefit of bendamustine vs. chlorambucil

This section begins with a summary of the submitted systematic review of cost-effectiveness studies and description of the methods used in the economic evaluation (Section 5.1, p47). This is followed by a critique of economic evaluation methods (Section 5.2, p68) and description of results (Section 5.3, p85). The ERG's findings are summarised in Section 5.4, p87. Section 6, p90 presents alternative base case ICERs and several important scenario analyses.

5.1 Overview of manufacturer's economic evaluation

5.1.1 Systematic review of cost-effectiveness studies

5.1.1.1 Description and appropriateness of manufacturer's search strategy

Search strategies were performed in the following databases on 4th June 2010:

- Medline
- Medline In Process
- Embase
- EconLIT
- NHS EED

The Medline, Medline in Process and Embase search strategies combined CLL disease terms with cost-effectiveness search terms and specific drug terms for bendamustine. The EconLIT and NHS EED databases were searched using disease terms only. All search syntax is shown in Section 9.10 (p213) of Napp's report.

All the combination of terms in the search strategies to define the chronic lymphocytic leukaemia population and the resources used were appropriate and replicable. There were some discrepancies in the resulting hits which could have been accounted for given the search date and database/interface used. The thesaurus terms related to modelling and cost-effectiveness are limited but adequate and considered reasonable in the context of this submission.

5.1.1.2 Search results

No cost-effectiveness studies were identified that are relevant to the appraisal of bendamustine for CLL (Source: Napp Submission, Section 6.1.2, p73). However, the ERG identified a recent poster reporting a cost-effectiveness study of bendamustine versus alemtuzumab and chlorambucil for CLL, presented at the 15th International Society for Pharmacoeconomics and Outcomes Research (ISPOR) annual international meeting in 2010.[25] Using a discrete event simulation, taking a US payer perspective, the incremental cost-effectiveness ratio (ICER) for bendamustine versus chlorambucil was $50,800 per QALY, or approximately £33,000 per QALY assuming an exchange rate of £1 = $1.56 (as at 17th September 2010).

5.1.2 Submitted economic evaluation

The economic evaluation submitted reports cost per QALY estimates for bendamustine versus chlorambucil for the first line treatment of CLL in patients who are unfit for fludarabine-based therapies. The model is written in Microsoft Excel, and described in detail in Section 6 (page 73) of the submission. Here, the main features of the model are summarised.

5.1.3 Natural history

Broadly speaking, the structure of the model is typical of many models for haematological malignancies, in that health states of PFS and progressive disease (PD) are modelled. However, the submitted model is more sophisticated than others previously reviewed by the ERG in two respects:

- Progression-free survival is divided according to responses status, employing SD, PR and CR states. The depth of response influences the quality of life weights

applied to time spent in these states (better response using higher utility) and the disease-management costs (better response using lower costs).

- Re-treatment with first line therapy may be followed by second line treatment with fludarabine plus cyclophosphamide (FC) therapy.

The submitted model uses a Markov cohort approach to model the natural history and treatment using the health states shown in Figure 7 and Figure 8 below. The treatment pathways modelled in the analysis were defined using national and local management guidelines and consultation with five haematologists involved in the treatment of CLL in England and Wales (Source: Napp Submission, Section 6.2.3, p78).

Figure 7. Treatment pathways assumed in the model

†By this stage, patients may be considered strong enough to try treatment with a fludarabine regimen. FC = fludarabine plus cyclophosphamide
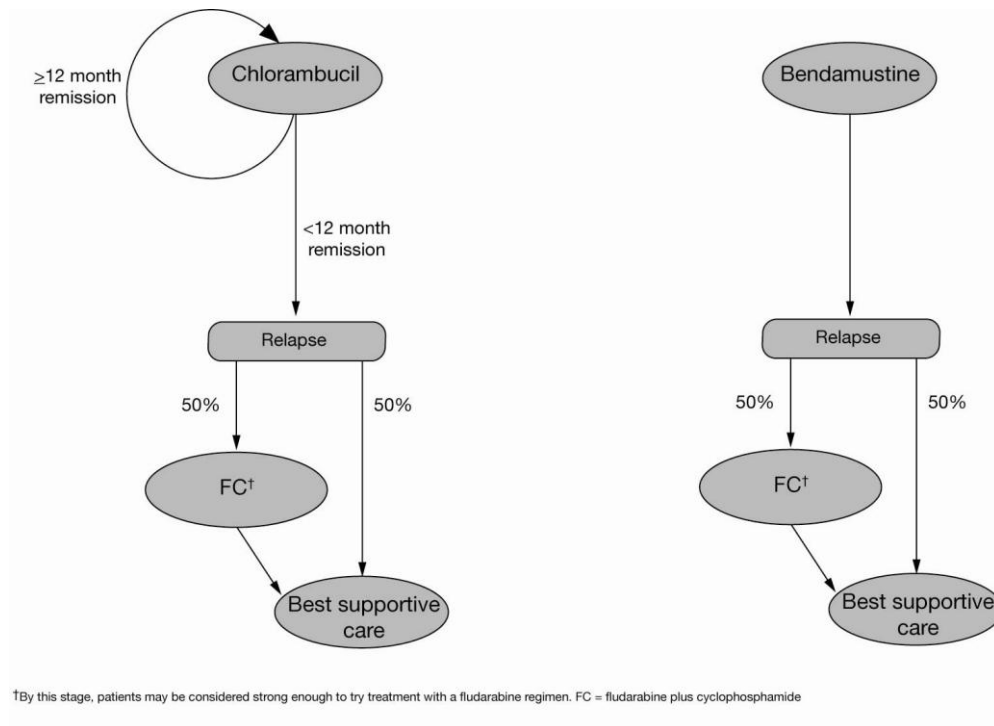
(Source: Napp Submission, Section 6.2.2, Figure 6.1, p76)

Figure 8. Schematic of model structure
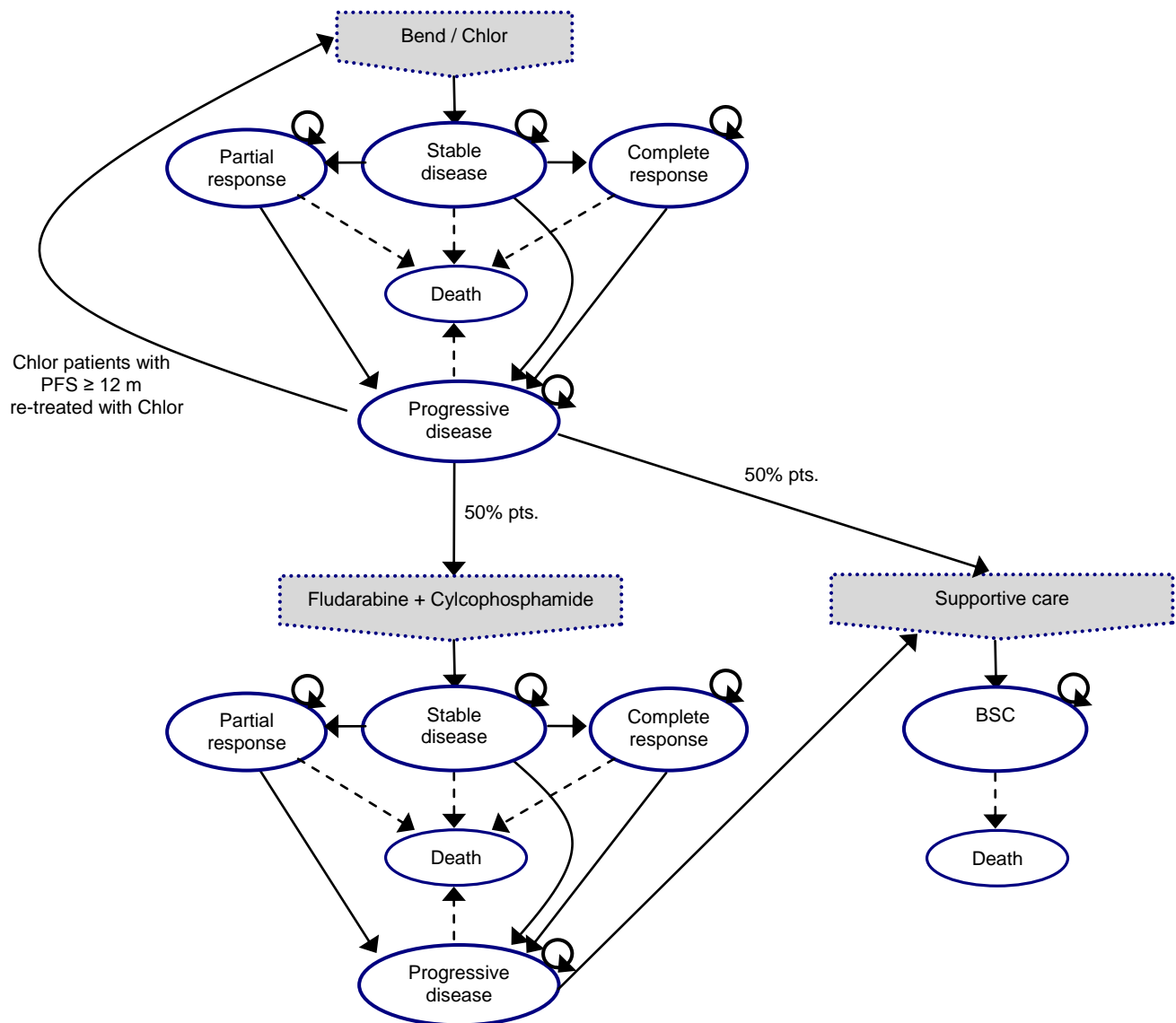
(Source: Napp Submission, Section 6.2.2, Figure 6.2, p77)

Hypothetical patients begin treatment on bendamustine or chlorambucil. Following first line treatment, patients who remain progression-free for at least 12 months on chlorambucil are re-treated after they progress. In the base case, it is assumed that patients can only be treated once with bendamustine. Patients who progress within 12 months on chlorambucil, or all patients treated with bendamustine who progress regardless of duration of response, have a 50% probability of receiving either a

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fludarabine plus cyclophosphamide (FC) based regimen or best supportive care (BSC). Patients in BSC are assumed to receive no active therapy. Patients who receive FC move to BSC after further progression on second line therapy. It is stated that it may seem counter intuitive that patients receive fludarabine second line, given that bendamustine is licensed specifically for patients who are not fit enough for fludarabine. However, a clinical advisory board convened by Napp with UK clinical experts confirmed that some patients would be expected to receive fludarabine second line, if their clinical condition had improved sufficiently following first line therapy (Source: Napp Submission, Section 6.2.3, p78–79). The ERG has confirmed with its clinical advisor that this is a realistic scenario in UK practice.

All patients begin treatment (with either chlorambucil or bendamustine) in the stable disease (SD) health state. In the next model cycle (after three months), they are allocated to their best overall response state: SD, PD, PR, or CR. The CR health state includes patients with a CR and nodular PR (previously named nodular complete responders). The submission states that this is in accordance with the definition from the National Cancer Institute Working Group criteria on CLL which defines patients with complete remission and persistent bone marrow nodules as nPR. Patients who enter SD, CR or PR then face a probability of progressing. Patients with PD may face second line treatment, where they then face the same possible transitions, or moving to BSC, where they remain until death.

A large number (39) of health states are required to model the above transitions. These are split into three groups: first line, first line re-treatment, and second line treatment. As noted, first line health states are SD, PR, CR and PD. The re-treatment health states comprise 28 states which capture whether the patient is in the first or second three months of re-treatment; and the specific time they have been in each of the states SD, PR, CR, PD during re-treatment. The second line group is sub-divided in to the following states: active treatment with FC, SD, PR, CR, PD, and BSC (assumed equivalent in cost and quality of life to PD following second line treatment). In the model, the depth of response influences the utilities (better response, higher utility) and the disease-management costs (better response, lower cost).

Overall survival (OS) is modelled by analysis of individual patient data from the pivotal RCT, and extrapolated beyond the follow-up period observed in the RCT (Source: Napp Submission, Section 6.3.1, p93–94).

The costs and disutilities associated with adverse events for first and second line therapies are modelled (Source: Napp Submission, Section 6.3, p94–97).

The time horizon is 35 years, the model cycle length is three months, and a half cycle correction is applied.

Study population and subgroups

The submission claims that the study population is typical of patients expected to receive bendamustine in the UK (Source: Napp Submission, Section 6.2.1, p74). The submission notes that patients treated with chlorambucil in the UK have widely varying age, co-morbidities and performance status. In the RCT, 51% of patients were aged <65 years and 49% were aged ≥65 years, and there was a range in patients' WHO performance status (67% with WHO 0, 28% with WHO 1 and 3% with WHO 2).

In addition to an estimate of cost-effectiveness of bendamustine for the overall population, estimates are presented for three subgroups (Source: Napp Submission, Section 6.9, p145–147):

- Age ≥ 65 years

- WHO physical status ≥ 1

- WHO physical status ≥ 1, and age ≥ 65 years.

The model incorporates two alterations to the analysis for the entire population to explore cost effectiveness in these subgroups. First, response rates reported for each subgroup are applied. Second, a dummy covariable is included for the subgroup in all survival analyses. All survival analyses used the parametric distributions from the base case. It was found that the treatment effect of bendamustine was maintained across subgroups (Table 7).

Table **7**. Odds ratios for overall response

Patient group	Absolute response probability (Chlorambucil), mean (95% CI)	Odds ratio for overall response (Bendamustine *vs.* Chlorambucil), mean (95% CI)
Base case (ITT)	35% (27%, 43%)	5.38 (3.26, 9.05)
Age≥65	36% (26%, 47%)	4.57 (2.25, 9.60)
WHO≥1	24% (13%, 38%)	4.67 (1.83, 12.65)
Age≥65 & WHO≥1	24% (11%, 43%)	3.94 (1.17, 14.71)

(Source: Napp Submission, Section 6.9.4, Table 6.34, p46)

The model does not present subgroup analyses based on chromosomal markers which have been associated with CLL prognosis, reporting that information on such markers was not collected during the RCT (Source: Napp Submission, Section 6.2.1, p75).

5.1.4 Treatment effectiveness

5.1.4.1 Response rates and PFS (first line bendamustine / chlorambucil)

Response rates used in the economic analysis are summarised in Table 8. Patients with an unconfirmed response were classified as having SD. Patients for whom no examination data were available (14 in the bendamustine arm and 19 in the chlorambucil arm) were not included in the initial response or time to progression analyses (Source: Napp Submission, Section 6.3.1, p83).

Table **8**. Best overall response to first-line treatment

Treatment		Stable disease (SD + unconfirmed response)	Partial response (PR)	Complete response (CR + nPR)	Progressive disease (PD)
Bendamustine (n=148)	n	23 (19 + 4)	43	67 (50 + 17)	15
	%	**16**	**29**	**45**	**10**
Chlorambucil (n=138)	n	37 (32 + 5)	41	7 (3 + 4)	53
	%	**27**	**30**	**5**	**38**

Source:Napp Submission, Section 6.3.1, Table 6.2, p84)

Parametric survival analyses were fitted to the RCT data to estimate the differential time to progression of patients with CR, PR and SD. Four parametric distributions were used for each survival analysis (exponential, Weibull, log-normal, log-logistic) and models were run with a treatment covariate (Source: Napp Submission, Section 6.3.1, p84). The treatment covariate was retained regardless of significance, to capture the differences between treatments observed in the trial. Uncertainty around the treatment effects is reflected in the probabilistic sensitivity analysis.

Selection of preferred distributions for use in the base case cost effectiveness analysis was based on visual comparison of empirical and fitted survival curves and comparison across models using Akaike's Information Criteria with $\alpha=3$. Sensitivity analyses are presented using different parametric models.

Details of the results of the comparison of curve fits are reported in Section 6.3.1 of the submission (p83–97). In summary:

- **For patients with SD**, the log-logistic distribution was chosen, and the ERG agrees that this provides a reasonable fit to the empirical data. Little evidence for different times to progression by treatment was found. The median time to progression was approximately one year.

- **For patients with PR**, the log-normal distribution was chosen, and the ERG agrees that this provides a reasonable fit to the empirical data. The median time to progression for bendamustine, approx. 1.8 years, is far greater than the median time for chlorambucil, approx. 1.1 years.

- **For patients with CR**, the log-normal distribution was chosen, and the ERG agrees that this provides a reasonable fit to the empirical data. The median time to progression for bendamustine, approx. 2.7 years, is far greater than the median time for chlorambucil, approx. 1.4 years.

Hence, not only does bendamustine yield greater response rates than chlorambucil, it also increases progression-free time given their health state, for patients with PR or CR. Better response rates tend to give longer time to progression.

5.1.4.2 *Time to treatment re-initiation following progression: all treatment lines*

The time to treatment re-initiation is used to inform the probability of being re-treated following progression on first line treatment, the probability of receiving second line FC following progression on re-treatment or first line treatment, and the probability of entering BSC following progression on second line therapy (Source: Napp Submission, Section 6.3.1, p88). The time to treatment re-initiation is modelled using an exponential curve, fitted to data from the RCT. From the information provided, the ERG calculates a median time to treatment re-initiation of approx. one year.

5.1.4.3 *Response rates and PFS (re-treatment with first line therapies)*

For treatment administered following the first progression event, no efficacy data (response or time to progression) are available from the RCT (Source: Napp Submission, Section 6.3.1, p89). Data regarding the efficacy of re-treatment and second line FC were therefore taken from the literature. A systematic review was carried out to identify papers reporting response, PFS or safety data for CLL patients receiving: bendamustine or chlorambucil (+/- prednisone) as re-treatment; or FC (+/- rituximab) after an alkylating agent.

Two relevant studies were identified reporting the results of repeat treatment – both concerning chlorambucil + prednisone. The study by Robak and colleagues (2005) was

used in the base-case analysis (Source: Napp Submission, Section 6.3.1, p89). No data describing repeat bendamustine treatment were identified (re-treatment with bendamustine is modelled in a sensitivity analysis). Use of the data from Robak and colleagues (2005) was complex and involved:

- Estimation of response rates on re-treatment

- Estimation of PFS by response to re-treatment.

Re-treatment response rates were calculated by applying the odds ratio (0.70) comparing overall response in previously treated and treatment-naïve patients from Robak and colleagues (2005) with the overall response rates used in the model for first line treatment (taken from the main RCT). In the base case, this approach was used only for the chlorambucil arm, as no bendamustine re-treatment was assumed. Assuming their method, we agree with Napp's estimated response rates on re-treatment for chlorambucil of CR = 4%, PR = 23%, SD = 30%, PD = 43% (Source: Napp Submission, Section 6.3.1, Table 6.9, Page 91).

PFS conditional on response is not available from Robak and colleagues (2005) or elsewhere. The model takes the following approach. Median estimates for PFS from Robak and colleagues (2005) for first line (17 months) and re-treatment with chlorambucil plus prednisone (12 months) are used to infer response-specific PFS as follows:

i. A hazard ratio for re-treatment vs. first line treatment PFS was derived from the median estimates from Robak and colleague (2005). This was applied to the treatment-specific first line median PFS from the main RCT (21.6 months for bendamustine; 8.3 months for chlorambucil). This provides estimates of median PFS at re-treatment for chlorambucil and bendamustine.

ii. Response-specific PFS were then generated using hazard ratios describing differences in PFS across response categories and by constraining median PFS for all response categories to the values generated in Step (i). The hazard ratios were estimated from the main RCT by analysing both arms pooled together using a proportional hazards model.

5.1.4.4 Response rates and PFS (second line fludarabine-cyclophosphamide)

The literature review referred to above identified 10 studies reporting efficacy data for FC administered without rituximab (Source: Napp Submission, Section 6.3.1, p92). It was found that many studies included a significant proportion of patients receiving FC as a third or subsequent line treatment and did not report separate outcomes for second line use and/or report results in the relevant population for small numbers of patients. Conversely, the submission states that the RCT described by Robak and colleagues (2010) includes many patients who have received only one previous treatment and reports response and PFS for 276 patients receiving FC. This study was therefore used in the economic model. Response rates from Robak and colleagues (2010) were: CR = 15%, PR = 53%, SD = 26%, PD = 6%.

A similar approach was used to estimate response-specific PFS as described for re-treatment above. Response-specific PFS were generated using the hazard ratios describing differences in PFS across response categories from the main RCT, and by constraining median PFS for all response categories to the values generated from Robak and colleagues (2010), see Napp Submission (Section 6.3.1, p104) for details. Given the results reported in the submission (Section 6.3.1, Table 6.11, p105), the ERG calculates median PFS time under FC treatment as 5.7 years for CR, 1.8 years for PR and 0.9 years for SD.

5.1.4.5 Overall survival

A Weibull distribution gave the best fit to the overall survival data from the RCT (Source: Napp Submission, Section 6.3.1, p93). A comparison of the empirical fitted survival curves is given in Figure 9 below.

Figure 9. Comparison of empirical and fitted overall survival curves

(Source: Napp Submission, Section 6.3.1, Figure 6.7, p94)

Median OS for bendamustine predicted by the model 8.3 years vs. not yet reached in the RCT. Predicted median OS for chlorambucil is 5.8 years vs. 5.5 years in the RCT. Despite the strong OS trend in favour of bendamustine, no statistically significant treatment difference has been shown to date. The submission suggests that this is probably because data are not sufficiently mature (Source: Napp Submission, Section 5.10.4, p69). The submission states a conviction that a statistically significant difference in OS will emerge with longer follow-up because previous studies have shown an association between improved response status and overall survival in CLL, noting that bendamustine significantly improves responses (Source: Napp Submission, Section 5.10.4, pp70, 72). Also, the relationship between greater OS for patients with better responses (CR and nPR) is noted to have been shown already in the RCT, being statistically significant at 54 months for responders (Source: Napp Submission, Section 5.10.4, p71).

In the model, the probability of death is assumed to be independent of health state.

5.1.5 Adverse events

Costs and disutilities associated with adverse events are modelled for first and second line treatment (Source: Napp Submission, Section 6.3.1, p94–95). For first line treatment and re-treatment, adverse events and proportions of patients experiencing them are shown in Table 9. Most adverse events in the main RCT were haematological, and were more common for bendamustine than for chlorambucil. The proportions of patients in each treatment arm with haematological adverse events were not modelled. Instead, the proportions of cycles in each arm when G-CSFs, erythropoietin, and red blood cells were used were modelled. The following criteria guided selection of adverse events for inclusion in the model:

- Grade 1–2 and trial arms differed by ≥5 % in % of patients experiencing event

- Grade 3–4 and trial arms differed by ≥2% in % of patients experiencing event.

These criteria were then modified. For example, Grade 3–4 pyrexia and pneumonia did not meet the criteria but were included, as treatment-related infections are known to be an important cause of morbidity and mortality in people with CLL.

Table **9**. Adverse event data: first line treatment / re-treatment

	Bendamustine	Chlorambucil
Number of patients in safety analysis	161	151
Total number of cycles of treatment received	783	733
Neutropaenia / thrombocytopaenia / leukopaenia / lymphopaenia:		
Granulocyte colony stimulating factors	3% of cycles	0.3% of cycles
Erythropoietin	0.5% of cycles	0.3% of cycles
Red blood cells	5.7% of cycles	2.1% of cycles
Grade 1–2 nausea only (nausea – vomiting)	4.4% of patients (18.7–14.3%)	6.6% of patients (13.2–6.6%)
Grade 1–2 nausea and vomiting	14.3% of patients	6.6% of patients
Grade 3–4 anaemia	2.5% of patients	0% of patients
Grade 3–4 pyrexia	1.9% of patients	1.3% of patients
Grade 3–4 pneumonia (infection)	1.9% of patients	0% of patients
Grade 1–2 diarrhoea	8.7% of patients	4% of patients

(Source: Napp Submission, Section 6.3.1, Table 6.13, p96)

Given that only the proportions of patients experiencing each adverse event are available (rather than the total number of adverse events experienced), the following assumptions are made in the submitted model:

- Patients who experience Grade 3–4 anaemia, Grade 1–2 nausea, Grade 1–2 nausea/vomiting or Grade 1–2 diarrhoea experience these in every cycle in which they receive treatment.

- Patients who experience Grade 3–4 pyrexia or Grade 3–4 pneumonia experience these only once during the course of treatment.

The adverse event rates for second line treatment with FC were taken from Robak and colleagues (2010) [26] and were modified slightly to give the values in Table 10.

Table 10. Adverse events with second line FC treatment in base case

	Number of patients experiencing event	
	Grade 1–2	Grade 3–4
Nausea (Grade 1 or 2 = nausea – nausea/vomiting)	45	–
Nausea/vomiting (Grade 1 or 2)	51	–
Anaemia (Grade 3 or 4)	–	35
Pyrexia (Grade 3 or 4)	–	42
Pneumonia (Grade 3 or 4)	–	17
Diarrhoea (Grade 1 or 2)	32	–
N	272	

(Source: Napp submission, Section 6.3.1, Table 6.14, p97)

5.1.6 Health related quality of life

Quality of life data was collected in the pivotal RCT using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC-QLQ-C30). Data were collected at baseline and at the end of each treatment cycle (up to six cycles). Since the duration of follow-up was short, it was not possible to analyse the long-term consequences of treatment on health related quality of life (HRQL) directly

from the trial. Baseline utility in the model of 0.70 (s.e. = 0.01, n=242) was estimated from the main RCT using a published mapping algorithm to convert the EORTC-C30 data to EQ-5D utilities, see the Napp Submission (Section 6.4.4, p107) for details. This baseline utility was used to estimate (a) the utility for the treatment period, applying utility decrements for adverse events; and (b) as the reference value to which utility decrements and increments associated with different health states were applied. As noted earlier, overall quality of life (as measured by the EORTC global health status question) was modestly improved in both groups during treatment, with no significant differences between the groups (Source: Napp Submission, Section 5.5, p54).

The submission reports a literature search carried out for utilities in CLL, including those used in pervious NICE STAs on drugs for CLL. This was used to select utilities for the period after treatment has stopped in the model, see the submission (Section 6.4.5, p120) for details. Studies had a range of limitations including: based on different conditions; e.g. non Hodgkin's lymphoma, very small sample sizes, poor quality, based only on expert opinions, not distinguishing between complete and partial responses, lack of toxicity data, and lack of detailed description of study.

Utility data incorporated in the model for patients after treatment are based on data from Beusterien and colleagues (2010),[9] a study commissioned by Napp. Utilities were elicited from 93 members of the UK general population by one-on-one, in person interviews using the standard gamble method. This sample valued twelve vignettes describing clinical endpoints reported in the main RCT of bendamustine, including CR, PR, SD and PD (see Appendix B, p100). Health states for second and third line treatment were included in the vignettes to capture the observation that, even when conditioning on response achieved, patients receiving later line therapy were likely to experience worse health outcomes. The health state descriptions were developed from information from the literature, patient web-based discussion forums, five UK CLL patients and four haematologists. The following domains were described: cancer description, 'cancer of the blood'; treatment response category; swollen glands in neck, armpits, or groin; limitations in performing daily activities; level of fatigue; appetite; and trouble sleeping because of night sweats.[9]

The unadjusted utilities shown in Table 11 were adjusted for use in the model as described below. The final adjusted utilities used for both treatment arms in the are given in Table 12

Table 12.

- Patients with an AE experience a utility decrement equal to the difference between the 'Stable disease + adverse event' valuation and the 'Stable disease' valuation from Beusterien and colleagues (2010) regardless of their health state.

- After the 4.9 month treatment period, the impact of different response states on utility is applied as an increment or decrement to the baseline utility from the RCT. The increments and decrements are calculated from Beusterien and colleagues (2010) as the difference between the SD state from Beusterien and colleagues (2010) and the relevant response state from Beusterien and colleagues (2010). For example, a person achieving a CR to first line treatment would have a utility of 0.70 (baseline from RCT) + 0.91 (CR Beusterien and colleagues) – 0.78 (SD Beusterien and colleagues) = 0.83.

- The utility for patients who are re-treated depends on response to re-treatment. The utility is calculated as the product of the value for stable disease and the proportion of the second cycle treated plus the product of the utility for the appropriate response (e.g. PR, CR, PD) and the proportion of the second cycle not treated, with the decrement corresponding to the difference in the SD utility from Beusterien and colleagues (2010) and the baseline utility from the RCT.

- Patients receiving FC or BSC experience a utility decrement equal to the difference between the 'Stable disease + second line treatment' valuation and the 'Stable disease' valuation, regardless of their response status. This is in addition to the decrement representing the difference between stable disease in first line and baseline utility from the RCT, described above.

- Patients on BSC were all assumed to experience the PD utility. The two decrements in the last point were then applied.

Table 11. Raw utilities before adjustment

Health state	Mean + SD	95% CI	Source
During treatment (baseline utility)	0.70 +0.22	0.67, 0.73	Utility study in main RCT
Complete response	0.91 + 0.11	0.88, 0.93	Beusterien *et al.* (2010)
Partial response	0.84 + 0.14	0.81, 0.87	Beusterien *et al.* (2010)
Stable disease	0.78 + 0.14	0.75, 0.82	Beusterien *et al.* (2010)
Progressive disease	0.68 + 0.20	0.64, 0.72	Beusterien *et al.* (2010)
Stable disease + 1–2 nausea	0.73 + 0.17	0.69, 0.76	Beusterien *et al.* (2010)
Stable disease + 1–2 nausea/vomiting	0.73 + 0.16	0.69, 0.76	Beusterien *et al.* (2010)
Stable disease + 1–2 diarrhoea	0.70 + 0.19	0.66, 0.74	Beusterien *et al.* (2010)
Stable disease + 3–4 anaemia	0.69 + 0.18	0.65, 0.72	Beusterien *et al.* (2010)
Stable disease + 3–4 pyrexia	0.67 + 0.17	0.63, 0.70	Beusterien *et al.* (2010)
Stable disease + 3–4 pneumonia	0.58 + 0.19	0.54, 0.62	Beusterien *et al.* (2010)
Stable disease + second line treatment	0.71 + 0.17	0.68, 0.75	Beusterien *et al.* (2010)

(Amended from: Napp Submission, Section 6.4.9, Table 6.18, p113)

Table 12. Adjusted utilities used in the model

Health state	Mean utility
First line (Bendamustine / chlorambucil)	
Complete response	0.83
Partial response	0.76
Stable disease	0.70
Progressive disease	0.60
First line re-treatment	
Retreatment (first three months re-treatment)	0.70
Stable disease (second three months re-treatment)	0.70
Stable disease (after re-treatment stopped)	0.70
Partial response (second three months re-treatment)	0.72
Partial response (after re-treatment stopped)	0.76
Complete response (second three months re-treatment)	0.75
Complete response (after re-treatment stopped)	0.83
Progressive disease (second three months re-treatment)	0.66
Progressive disease (after re-treatment stopped)	0.60
Second line (FC)	
FC (during active treatment)	0.63
Stable disease	0.63
Partial response	0.69
Complete response	0.76
Progressive disease	0.53
BSC	0.53

5.1.7 Resource use and costs

Costs are estimated from the NHS and PSS perspective, and are for drug acquisition, drug administration, disease management (such as haematologist visits, blood tests, blood transfusions), and AEs (Source: Napp Submission, Section 6.5, p116–126). Costs are split according to whether they accrued during or after treatment on bendamustine, chlorambucil or fludarabine / cyclophosphamide.

5.1.7.1 Drug acquisition costs, drug administration costs and other costs whilst on treatment

Drug acquisition costs

In the model, bendamustine is administered at a dose of 100 mg/m^2 body surface area on Days 1 and 2 of each 28-day cycle. Patients are given bendamustine for a mean of 4.9 treatment cycles, as in the main RCT. The average body surface area is assumed to be 1.72 m^2 (Source: Napp Submission, Section 6.5.5, Table 6.19, p120). The following costs for bendamustine are reported: 25 mg x 5 = £347.26, 25 mg x 20 = £1,379.04, 100 mg x 5 = £1,379.04.[27] For bendamustine, the average price per mg across the three formulations, £2.76 / mg, is used in the model, as they are very similar across the formulations.

In the model, chlorambucil is administered at a dose of 0.8 mg/kg Broca's weight on Days 1 and 15 of each 28-day cycle. Patients are given chlorambucil for a mean of 4.9 treatment cycles, as in the main RCT. The average Broca's weight was assumed to be 68.73 kg (Source: Napp Submission, Section 6.5.5, Table 6.19, p120). The cost of chlorambucil acquisition is £8.36 for 25 x 2 mg and taken from the BNF.[28]

The acquisition costs of second line fludarabine and cyclophosphamide are modelled at doses of 25 mg/m^2 and 250 mg/m^2 respectively, on each of three days per treatment cycle, as in Robak and colleagues 2010 (Source: Napp Submission, Section 6.5.5, Table 6.19, p120). Patients are given fludarabine and cyclophosphamide for a mean of 4.6 treatment cycles, as in Catovsky and colleagues (Source: Napp Submission, Section 6.5.5, Table 6.19, p120). As for bendamustine, the average body surface area is assumed to be 1.72 m^2. The cost of fludarabine and cyclophosphamide is reported as 10 mg x 20 = £357.49 and 50 mg x 100 = £13.85 respectively, taken from the BNF.[28]

In the model, a dose intensity of 100% is implicitly assumed for all drugs. All drug costs are calculated assuming full wastage at the body surface area / Broca's weight for the average patient in the main RCT.

Drug administration costs

Bendamustine is administered intravenously over 30–60 minutes. The cost of the first administration is £272, and £226 for subsequent administrations (Source: Napp Submission, Section 6.5.5, Table 6.19, p120). All other drugs are taken orally and therefore incur no administration costs.

Other costs whilst on treatment

Napp commissioned an Advisory Board of five UK haematologists to investigate treatment pathways and estimate resource use for CLL. This informed assumptions for resource use whilst patients are receiving first and second line treatment: haematologist outpatient visits, blood counts, biochemistry and antiemetics. Patients on all drugs are assumed to have one haematologist outpatient visit per 28-day treatment cycle. The cost per visit is £209 for all drugs except bendamustine, for which the cost per visit is £131.

One blood count test (£2.97) and one biochemistry test (£1.34) per month are assumed for patients whilst on treatment. The costs of antiemetics were also modelled (Source: Napp Submission, Section 6.5.5, Table 6.19, p121).

5.1.7.2 Costs when not on treatment

Resource use when not on drug treatment (first or second line) was informed by clinical experts, and assumed independent of treatment arm. The frequency of haematologist visits (£131 per visit), full blood counts (£2.97 per test) and routine biochemistry (£1.34 per test) varied by response status: once per month for stable disease, once per three months for partial response, once per six months for complete response, and once per three weeks for progressive disease. In addition, a blood transfusion every three weeks was assumed for patients in progressive disease. Each transfusion comprises two units of red blood cells at £261, and the administration cost of a transfusion of £85.

5.1.7.3 Adverse event costs

The costs of treating adverse events are given in Appendix A, page 99.

5.1.8 Discounting

Future costs and benefits are discounted at 3.5% as specified in the NICE reference case.[29]

5.1.9 Sensitivity analyses

One-way sensitivity analyses are performed on numerous assumptions concerning the treatment effects, survival distributions, treatment pathways following first line therapy, data sources for subsequent line therapies, subsequent line therapy efficacy, utilities, costs, and response rates (Source: Napp Submission, Section 6.6, p126–135).

Numerous parameters were included in the probabilistic sensitivity analysis (see Napp Submission, Section 6.6, p126–135 for a comprehensive list). All important parameters seem present in the analysis. Examples are given in Table 13.

Table 13. Examples of important parameters in probabilistic sensitivity analysis

Parameter	Distribution
Best initial response rates	Dirichlet
PFS	multivariate normal
Time from progression to re-retreatment	normal
PFS from re-treatment	log-normal
Proportion of patients treated with FC/BSC second line	Beta
Median time to progression FC	Beta
Utilities	Beta
Resource use estimates (counts)	gamma
Resource use estimates (proportions)	Beta
Unit costs	gamma

A cost-effectiveness acceptability curve (CEAC) is presented and a scatter plot of incremental costs and QALYs on the cost effectiveness plane for the base case (Source: Napp Submission, Section 6.7.8, p142–143).

5.1.10　　　Model validation

The manufacturer has taken steps to validate and verify the submitted model (Source: Napp Submission, Section 6.8, p144). Validity was addressed in two ways. Firstly, the modelled response rates and PFS are compared to those from the RCT (Source: Napp Submission, Section 6.3.1, Figure 6.6, p88). Secondly, the submission states that the "overall survival benefit estimated in the model is similar to what patients would receive in the real life setting" (Source: Napp Submission, Section 6.8.1, p144) (although "overall survival benefit" is not clearly defined, and this statement is not justified). The performance of the model was verified by an academic group who audited the Excel model and a consulting firm who had audited an earlier version of the model.

5.2 Critique of economic evaluation

In this section, a critique of the submitted analysis is reported. First, the ERG considered the model against checklists of good practice (Section 5.2.1, p68). Then a critical appraisal of the model structure and data is reported in Sections 5.2.2 to 5.2.6, p72. In Section 5.3, p85, the results obtained from the submitted model are discussed.

5.2.1 Critical appraisal frameworks

The extent to which the economic evaluation meets the NICE reference case[29] is described (Table 14), and the evaluation is considered against two widely used quality tools for economic evaluations: Drummond and colleagues (1997)[30] (Table 15), and Philips and colleagues (2006)[31] (Table 16). The model generally satisfies the NICE reference case, except for some concerns about measurement of health-related quality of life. In the final table, we highlight concerns about the assumed hazard ratio for overall survival, the timings of blood transfusions, and the measurement of health-related quality of life.

Table 14. Critical appraisal checklist based on NICE Reference Case[29]

NICE reference case requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	✓	
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	✓	Comparator is chlorambucil, which is the only comparator treatment considered in the scope
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	✓	One RCT of bendamustine vs. chlorambucil.
Measure of health benefits	QALYs	✓	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Partially	In the RCT, used for HRQL during treatment, data are taken directly from patients for the estimates of baseline utility using EORTC-QLQ-C30 and mapped to EQ5D. Health states for responses to treatment , programme disease of adverse events were described by vignettes developed from a range of sources.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Partially	QoL data in RCT mapped to EQ-5D, as required. However, after treatment, utilities were elicited using a vignette approach, whereas the generic EQ-5D measure is preferred.
Discount rate	3.5% pa for costs and health effects	✓	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓	

Table 15. Critical appraisal checklist from Drummond and colleagues[30]

Item	Critical appraisal	Reviewer comment
Is there a well defined question?	✓	
Is there a clear description of alternatives (i.e. who did what to whom, where, and how often)?	✓	Bendamustine v. chlorambucil for 1st-line treatment of chronic lymphocytic leukaemia for patients unsuited to fludarabine
Has the correct patient group / population of interest been clearly stated?	✓	Patient group from main RCT assumed to be similar to patients in actual practice.
Is the correct comparator used?	✓	Chlorambucil, as defined in scope.
Is the study type reasonable?	✓	Transition probability cost-utility model
Is the perspective of the analysis clearly stated?	✓	UK NHS & PSS
Is the perspective employed appropriate?	✓	
Is effectiveness of the intervention established?	✓	The RCT shows a greater complete response rate, and PFS for bendamustine compared to chlorambucil.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	✓	35-year time horizon used in the model, after which time, virtually all modelled patients are dead. Hence the time horizon is effectively life time, and appropriate.
Are the costs and consequences consistent with the perspective employed?	✓	All costs from UK NHS & PSS perspective.
Is differential timing considered?	✓	
Is incremental analysis performed?	✓	
Is sensitivity analysis undertaken and presented clearly?	✓	Univariate and probabilistic sensitivity analyses presented.

Table 16. Critical appraisal checklist of Philips and colleagues (2006) [31] for model-based analyses

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Bendamustine v. chlorambucil for 1st-line treatment of chronic lymphocytic leukaemia for patients unsuited to fludarabine
S2	Statement of scope/perspective	✓	NHS and PSS perspective. Cost and benefit inputs are consistent with the perspective. Scope of model stated.
S3	Rationale for structure	✓	Cohort model is appropriate.
S4	Structural assumptions	✓	Model assumptions are explained clearly in the report. Overall, we are satisfied with the structural assumptions. Weibull functions were fitted to OS from the RCT, and a variety of functions fitted to PFS from the RCT.
S5	Strategies / comparators	✓	See S1.
S6	Model type	✓	Cohort model is appropriate.
S7	Time horizon	✓	35-year time horizon used in the model, after which time, virtually all modelled patients are dead. Hence the time horizon is effectively life time, and appropriate. Since OS is fairly immature, extensive extrapolation is necessary.
S8	Disease states / pathways	✓	We are broadly satisfied with the choice of treatment pathways, including re-treatment with 1st-line drugs, and 2nd-line treatment with FC. Many (39) health states are modelled which consist of several states for CR, PR, SD and PD, re-treatment, and 2nd-line therapy.
S9	Cycle length	✓	Three months is appropriate.
Data			
D1	Data identification	✓	Data identification methods are well described.
D2	Pre-model data analysis	✓	Method of fitting clinical effectiveness data (PFS and OS) by regression models, estimation of resource costs, and estimation of utilities from RCT combined with study elicited from general population is well described.
D2a	Baseline data	✓	Baseline data for chlorambucil from the RCT is appropriate.
D2b	Treatment effects	?	Treatment effects of bendamustine vs. chlorambucil, in terms of hazard ratios for PFS and OS taken from the main RCT, as appropriate. However, we do not agree with Napp's hazard ratio for OS of 1.66. Instead, the most recent data yields a hazard ratio of 1.3 (Section 5.2.4, p76).
D2c	Quality of life weights (utilities)	?	Health-related quality of life was recorded in the RCT whilst patients on treatment. Utilities whilst patients off treatment taken from independent vignette-based study, with measurement of HRQL from general public. In the

Dimension of quality			Comments
D3	Data incorporation	?	RCT, used for QoL during treatment, QoL data taken directly from patients, as required. However, after treatment, QoL elicited from members of UK public. However, NICE reference case is to elicit QoL from patients/carers. QoL data in RCT mapped to EQ-5D, as required. However, after treatment, utilities were elicited using a vignette approach, whereas the generic EQ-5D measure is preferred (Section 5.2.5, p79). Data incorporated in the model is referenced, well described and transparent. For the PSA, the choice of distribution for each parameter has been described and justified. However, we do not agree with Napp's assumption for the timing of blood transfusions (Section 5.2.6.2, p83).
D4	Assessment of uncertainty	✓	Most types of uncertainty assessed.
D4a	Methodological	✓	Single type of model, which is adequate.
D4b	Structural	✓	Some structural sensitivity analyses performed.
D4c	Heterogeneity	✓	Subgroups based on age and WHO status modelled.
D4d	Parameter	✓	Probabilistic and univariate sensitivity analyses performed appropriately.
Consistency			
C1	Internal consistency	✓	Although Napp's model is very detailed and complex, we found no logical errors in the model. Napp state that the model was audited by an academic team and a consulting firm.
C2	External consistency	✓	Napp compare the modelled PFS and OS against that experienced in the main trial.

Notes: ✓ indicates 'no concerns'; X indicates 'concerns'; ? indicates 'some concerns'

5.2.2 Critical appraisal of modelling approach and structure

As stated in Section 5.1.3, p48, the model is more sophisticated than other cost-effectiveness models evaluating drugs for haematological malignancy seen by the ERG in that progression-free survival accommodates different levels of response (SD, PR and CR), and subsequent, second line FC therapy is modelled.   However, the ERG is not convinced that the degree of sophistication, with the use of 39 health states, is justified by the quality of the data. Many assumptions are required to implement the model, regarding parameters such as response rates to re-treatment, time to progression after re-treatment, response rate to FC second line treatment, time to progression after FC

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treatment, proportion of patients receiving second line FC treatment, and the nature of second line treatment.

The ERG has confirmed that that the treatment pathways shown in Figure 7 and Figure 8, involving re-treatment and second line treatment with FC are reasonable. However, the ERG disagrees with the submission around subsequent treatment after first progression and suggests that 80% of people would proceed to second line therapy (50% of patients proceed to BSC in the model) and that not all patients would receive FC as second line therapy, as assumed in the submitted model.

The time horizon of 35 years, the model cycle length of three months, and the use of a half-cycle are considered by the ERG to be appropriate for the decision problem.

Second line therapies

In the RCT, 49% of patients in the bendamustine arm, and 63% in the chlorambucil arm took second line drug therapy after progression (Source: Napp Submission, Section 5.10.4, p71). Furthermore, a higher proportion of patients in the chlorambucil arm were given second line drugs compared to patients initially on bendamustine (e.g. 29% of chlorambucil patients took bendamustine-based therapies versus 13% of bendamustine patients, 13% of chlorambucil patients took rituximab-based therapies versus 5% of bendamustine patients, and 33% of chlorambucil patients took fludarabine monotherapy versus 23% of bendamustine patients). As suggested by the manufacturer, this may dilute the survival advantage of bendamustine in the RCT (Source: Napp Submission, Section 5.10.4, p94).

The ERG suggests that the imbalance in the proportion of patients in the trial arms given second line drugs can be dealt with in any one of three ways for the purposes of modelling the cost-effectiveness of bendamustine;

1. Cost all the second line drugs received in each treatment arm in the RCT and model the actual, unadjusted overall survival from the RCT.

2. Do not cost the second line drugs received in the RCT, and estimate overall survival for each treatment arm using a method such as the Rank-Preserved Structural Failure Time (RPSFT) method, which estimates OS assuming no

second line drug treatment, as recently used in the NICE appraisal of sunitinib for gastro-intestinal stromal tumours.[32]

3. Do not cost the second line drugs received in the RCT. Instead, estimate the costs and utilities associated with the use of second line drugs likely to be used in actual clinical practice in the UK. The OS from the trial can only be used if we believe that the overall survival which would be achieved if these second line drugs were used is similar to the overall survival achieved in the RCT (which uses different second line drugs).

The submitted model uses the third option, where it is assumed that 50% of patients would be treated with FC as second line. The implicit assumption is that the use of FC would yield similar overall survival as achieved in the RCT (where different second line drugs were used). The ERG recognises that this is plausible. The ERG agrees with that the use of FC as second line is likely to improve quality of life. Therefore, the ERG is satisfied with the assumption of modelling re-treatment with first line drugs and treatment with second line FC without costing the second line drugs as received in the RCT.

Given that numerous assumptions are made regarding treatment efficacy and utilities with re-treatment and second line treatment with FC, for which limited evidence is available, the ERG has carried out sensitivity analyses where Options 1 and 2 above are explored.

Option 1: In this case, the first step is to set the costs of first line re-treatment and second line treatment with FC to zero, and all utilities after first line progression are set as 0.60. Technically, in the model, this is achieved by:

- setting the costs of fludarabine and cyclophosphamide, and the corresponding administration cost to zero and the costs of AEs for chlorambucil and FC to zero by changing cells H67 to AP71 to zero in worksheet 'Trans Mat', and setting the total cost (Row 66) equal to the sum of all costs (Rows 67 to 72).

- ideally, the utilities for patients on the second line treatments would be modelled from the RCT. However, given that this information is not available the ERG has assumed that all utilities for all re-treatment and second line health states are

> equal to the utility for PD after first line treatment = 0.60, by setting cells C40 to
> D54 to zero in worksheet 'InterimCalcs'.

With these assumptions, the base case ICER of £12,000 decreases marginally to £10,900 per QALY. Interestingly, the complex modelling of re-treatment and second line treatment has minimal impact on the cost-effectiveness of bendamustine. However, this figure does not incorporate two important pieces of data. First, the total per patient acquisition cost for second line drugs taken in the RCT is not known, because the mean dosage per patient by second line drug was not recorded in the study (Source: Napp second response to our requests for clarification). However, the total per patient cost of second line drugs will be higher in the chlorambucil arm than in the bendamustine arm because a greater proportion of chlorambucil patients received more expensive drugs. Accommodating this would reduce the ICER further below £10,900 per QALY. Conversely, the average quality of life of patients in the chlorambucil arm will increase more than for patients in the bendamustine arm because a greater proportion of chlorambucil patients received second line drugs. The ERG does not have data to address this issue, but it will increase the ICER. Overall, the ERG believes that the net effect would be to yield an ICER less than £10,900 per QALY, because any OS benefit from second line drugs are already reflected in the OS used in the model, and we believe that any additional QALY gains in the chlorambucil arm would be outweighed by the possibly substantial additional second line drug costs in the chlorambucil arm.

Option 2: Again the ERG has set the costs of re-treatment and second line treatment with FC to zero, and set all utilities after first line progression to 0.60. Next, an increased treatment effect is modelled in terms of the overall survival benefit of bendamustine over chlorambucil. Note that this approach is suggested as appropriate on p71 and p94 of the submission. As described above, this could be estimated using a method such as the RPSFT method. This therefore also yields an ICER of less than £10,900 per QALY.

Adverse events

The ERG is satisfied with the approach to modelling AEs in the economic evaluation submitted.

5.2.3 Patient group

The cost-effectiveness of bendamustine is presented for the following three subgroups: Age ≥ 65, WHO ≥ 1, and Age ≥ 65 WHO ≥ 1 combined. There is no independent source with which the ERG can check the subgroup-specific response data (**Table** 7, p4) and the subgroup-specific survival curves. The ERG has confirmed that the data presented in the submission are implemented correctly in the model. Although not stated, the model assumes the following hazard ratios for overall survival: 1.58 for Age ≥ 65, 1.61 for WHO ≥ 1, 1.61 for Age ≥ 65, WHO ≥ 1 combined, compared to the base case assumption of 1.66, see next section.

5.2.4 Treatment effectiveness data

The ERG is satisfied with the method of estimating the response rates and PFS for re-treatment.

Progression-free survival

The ERG is satisfied with the complex methods to estimate response rates and PFS for first line bendamustine / chlorambucil, time to treatment re-initiation following progression for all treatment lines, response rates and PFS for re-treatment with first line therapies, and response rates and PFS for second line fludarabine-cyclophosphamide (Section 5.1.4, p53).

The validity of the submitted model is explored by comparing modelled PFS with that from the RCT in Table 6.23, p136 of the submission. The modelled PFS agrees well with the RCT PFS for chlorambucil, but the modelled PFS is shorter-tailed compared with the RCT PFS for bendamustine (PFS at 1 year = 74% model, 80% RCT, at 2 years = 42% model, 49% RCT, at 3 years = 21% model, 30% RCT). If the modelled PFS were adjusted to fit the RCT PFS more closely, it is likely that the cost-effectiveness of bendamustine would improve slightly, because patients in the bendamustine arm would then spend longer in the higher utility PFS health states. However, the ERG considers that the impact of such an adjustment on the ICER is likely to be small.

Overall survival

OS is worthy of close scrutiny because it is a key driver of the cost-effectiveness of bendamustine. Whilst the curve fits shown in Figure 9, p58 above are implemented correctly in the model, the ERG has two important concerns with the modelled OS.

First, given that the overall survival data is immature, survival must be extrapolated over many years. This introduces considerable uncertainty into the modelled estimates of OS. Although the modelled survival fits available data reasonably, the extent to which the assumed function predicts events that have not yet been observed is unknown.

Second, the ERG believes that the modelled treatment effect, in terms of the hazard ratio of OS, is too high, and biases cost-effectiveness in favour of bendamustine. The modelled hazard ratio (not stated in the submission), is 1.66 (=exp(0.3611/0.7106), calculated by the ERG from the Weibull coefficients on p93 of the submission). However, the hazard ratio reported from the RCT is lower, at 1.45 (Source: Napp Submission, Section 5.5, p54). Furthermore, the hazard ratio based on the most mature data from the pivotal trial is 1.3. This more recent data was received by the manufacturer a few days before the assessment was submitted, and is based on a median observation time of 54 months, rather than the 35 months for data reported in the clinical effectiveness section of the submission (Source: Napp Submission, Section 6.10.5, p149). The ERG asked for more details of OS based on this more recent data, and received the Kaplan-Meier curves in Figure 10 below. In this figure, we see that the overall survival benefit of bendamustine is not as convincing as in the earlier data (Figure 9).

Figure 10. Updated overall survival from pivotal RCT
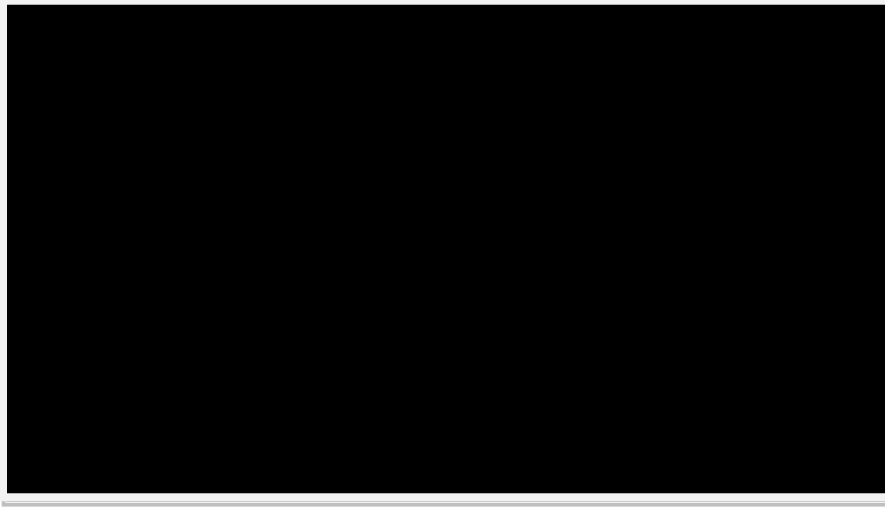
Whilst the hazard ratio 1.3, based on the most recent data, is known, the most recent estimates for OS in either of the treatment arms is not. However, the revised ICER, based on the updated hazard ratio of 1.3, is insensitive to the absolute OS for each treatment. For example, assuming chlorambucil OS is unchanged, but bendamustine OS becomes shorter-tailed, the base case ICER of £12,000 decreases to £11,700 per QALY, and the ICER assuming no blood transfusion costs (see Section 5.2.6.2, p83 below) increases from £7,000 to £9,700 per QALY. Technically, this is achieved by leaving the Weibull intercept parameter unchanged at 2.0203, and changing the treatment effect parameter from 0.3611 to 0.1864.[1] Henceforth, this is assumed by the ERG ██████████████████████████████████████

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[1] Alternatively, assuming bendamustine overall survival is unchanged, but chlorambucil overall survival becomes longer-tailed, the base case ICER of £12,000 remains unchanged, and the ICER assuming no blood transfusion costs increases from £7,000 to £9,300 per QALY. Technically, this is achieved by changing the intercept parameter to 2.1950, and changing the treatment effect parameter 0.1864.

It may seem paradoxical that the submitted base case ICER of £12,000 per QALY is almost unchanged when the hazard ratio is reduced from 1.66 to 1.3, whereas the ICER assuming no incremental blood transfusion costs increases substantially, from £7,000 to £9,700 per QALY. This is explained as follows. As expected, incremental discounted QALYs fall substantially, from 1.27 to 0.70 when the hazard ratio is reduced. However, the base case discounted incremental blood transfusion costs also decrease substantially, from £6,300 to £1,400. The net effect is to leave the base case ICER virtually unchanged. On the other hand, starting with the assumption of no incremental blood transfusion costs, whilst incremental QALYs again fall substantially, the incremental blood transfusion costs remain at zero when the hazard ratio reduces. Therefore, the ICER increases substantially, from £7,000 to £9,700 per QALY.

In the manufacturer's base case, patients are expected to spend more time in progressive disease (PD) in the bendamustine arm (7.8 years), compared to the chlorambucil arm (6.1 years). However, assuming the updated hazard ratio of 1.3, patients are predicted to spend a very similar time (approx. 6.1 years) in PD. It could be argued that the assumption of equal time in PD is a useful sensitivity analysis in its own right for the following reasons. First, Napp's estimates of OS are subject to much uncertainty because they have extrapolated over a long time. Second, this sensitivity analysis models the case when we suspect that bendamustine has no benefit over chlorambucil in terms of extending survival after treatment is stopped (of course, we still assume bendamustine extends PFS).

5.2.5 Health related quality of life

The ERG believes that it is appropriate to use the baseline utility of 0.70 estimated from the data collected during the main RCT. Although this is based on mapping between EORTC and EQ-5D, rather than on EQ5D data collected in the trial, this approach is supported within the NICE reference case.[29] We note that the mapping algorithm was derived using data from 199 patients with inoperable oesophageal cancer. EQ-5D utilities were regressed on EORTC-C30 responses (Source: Napp Submission, Section 6.4.4, p107). The ERG notes that there were many missing data points in the quality of life dataset in the main trial, with many patients not having the EORTC recorded for all six cycles. This has the potential to create bias as patients who left the study before

completion of six treatment cycles were more likely to be in a more severe health state (Source: Napp Submission, Section 5.10.3, p65–66). However, the extent of non-reporting of quality of life for those patients on treatment is not known, which is relevant to assessing the potential for bias in the utility estimate.

The submission bases the utilities for patients after treatment on data from Beusterien and colleagues (2010),[9] a study commissioned by the manufacturer. The ERG is generally satisfied with the use of this data for the cost-effectiveness model, given the absence of clearly superior alternative data. Furthermore, the cost-effectiveness of bendamustine appears relatively insensitive to the source of the. Nonetheless, it should be noted that the methods used by Beusterien and colleagues (2010) does depart from the NICE reference case[29] in that utilities were obtained using a vignette approach, and limited details are provided on the methods for generating the descriptions valued. Also, given that the vignettes state 'you have cancer', and although research on labelling of the underlying condition in a vignette is sparse, subject to methodological variation and somewhat contradictory, there is some evidence that labelling of a state as referring to cancer may result in lower utility estimates from non-sufferers.[33,34] Furthermore, utilities were elicited using the standard gamble method, rather than the time trade-off method (as used for the EQ5D). Although the reference case does not specify a preferred choice-based method for health state valuation, there is considerable evidence that the standard gamble yields generally higher estimates of preference than time trade-off.[35]

The utilities obtained from Beusterien and colleagues (2010) were elicited by members of the public living in England and Scotland. The mean utilities from Scottish people were statistically significantly ($p < 0.05$) higher than those from the English for many of the health states.[2,9] When the values elicited by those living in England only are used (59 out of the 89 respondents), the base case ICER increases only marginally, from £12,000 to £12,300 per QALY.

The ERG agrees with the approach used to model utilities after treatment according to response, by applying an increment or decrement to the baseline utility from the RCT.

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[2] stable disease higher by 0.07, progressive disease higher by 0.11, stable disease + grade 1-2 nausea higher by 0.08, stable disease + grade 1-2 nausea/vomiting higher by 0.08, stable disease + grade 3-4 anaemia higher by 0.08, stable disease + grade 3-4 pyrexia higher by 0.08, second line treatment higher by 0.08.

5.2.6 Resources and costs

5.2.6.1 Drug acquisition costs, drug administration costs and other costs whilst on treatment

Drug acquisition costs

The ERG is satisfied with the modelled dosing schedule of bendamustine and the assumption of a mean of 4.9 bendamustine treatment cycles per patient, as these are as experienced in the RCT. The ERG also agrees with the assumption of a mean body surface area of 1.72m^2. As a sensitivity analysis, the ERG assumed that all patients take the maximum of six cycles, and that this does not change the clinical effectiveness of bendamustine, the base case ICER increases from £12,000 to £13,300 per QALY.

The submission cites the following costs for bendamustine acquisition: 25 mg x 5 = £347.26, 25 mg x 20 = £1,379.04, 100 mg x 5 = £1,379.04. We asked the manufacturer for a reference for this information, and they replied by citing the Napp Trade Price List September 201027 (see Appendix B, page 100: Napp responses to queries from PenTAG). Napp say that bendamustine has only recently been launched, and is not yet included in the BNF[28] and MIMS.[36] However, we have confirmed the prices of bendamustine used in the submission from MIMS.[36]

The ERG is satisfied with the modelled dosing schedule of chlorambucil and the assumption of a mean of 4.9 treatment cycles per patient, as these are as experienced in the RCT. The ERG also agrees with the assumption of a mean Broca's weight of 68.73 kg. The assumed cost of chlorambucil of £0.17 per mg, is also confirmed from the BNF.[28]

As stated in the submission, there is no consensus on the appropriate dosing of chlorambucil. The SPC cites a different dosage schedule compared to the main RCT (and as modelled): *Initially Leukeran (chlorambucil) is given at a dosage of 0.15 mg/kg/day until the total leucocyte count has fallen to 10,000 per µL. Treatment may be resumed four weeks after the end of the first course and continued at a dosage of 0.1 mg/kg/day.[37]* According to the submission, while the total dose of chlorambucil per cycle is different under the SPC dosing (49 mg for second dose and further doses) compared

to the modelled dose (112 mg per cycle), the total dose per patient over the entire treatment period is similar (over 12 months, total dose 612.5 mg vs. over five cycles, total dose 560 mg).   Furthermore, the ERG consider that differences in dosing between that costed in the model and that realised in practice will have a negligible effect on the cost-effectiveness of bendamustine, because chlorambucil has a low acquisition cost (mean £150 per patient in submission base case). Finally, the ERG has received clinical advice that the dose of chlorambucil used in the RCT and as modelled compares reasonably with dosages currently used in NHS practice.

On a related matter, the submission states that there were some errors in the dosing of chlorambucil in the RCT (Source: Napp Submission, Section 6.2.7, p82). Specifically, in some cases the actual weight of the patient was used rather than Broca's weight when calculating doses of chlorambucil. Given that the mean actual weight per patient, 73.9 kg, is similar to the mean Broca's weight, 68.5 kg, the ERG consider that this error will have a negligible impact on the cost-effectiveness of bendamustine.

The ERG agrees with the assumed costs of FC therapy at £1.79 and £0.003 per mg respectively, taken from the BNF.[28] Fludarabine was modelled as being administered at a dose of 25 mg/m^2 on each of three days per treatment cycle, as in Robak and colleagues 2010 (Source: Napp Submission, Section 6.5.5, Table 6.19, p119), for a mean of 4.6 treatment cycles, as in Catovsky and colleagues (Source: Napp Submission, Section 6.5.5, Table 6.19, p120). However, this conflicts with the dose recommendation in the BNF[28] of 40 mg/m^2 for five days every 28 days, usually for six cycles. The total acquisition cost of fludarabine increases greatly under the BNF dosing, from £1,233 to £3,689 for those patients treated with fludarabine. Nonetheless, the cost-effectiveness of bendamustine is only marginally influenced implementing the dosage recommended in the BNF (setting aside possible influences on effectiveness), with the base case ICER increasing from £12.000 to £12,100 per QALY.

The submitted model implicitly assumes a dose intensity of 100% for both bendamustine and chlorambucil. However, the mean dose intensities in the RCT were 90% for bendamustine and 95% for chlorambucil (Source: Napp Submission, Section 5.10.4, p69).[24] The ERG asked the manufacturer to confirm this information, and to justify their modelling assumption of 100% dose intensity for both drugs. In response, the

manufacturer confirmed the dose intensities from the RCT and reported that the assumption of100% dose intensity was for simplicity (Source: Napp response to PenTAG queries, p11). The ERG agrees with the manufacturer that when dose intensities from the RCT are modelled, the base case ICER falls only slightly, from £12,000 to £11,600 per QALY.

Drug administration costs

The ERG is satisfied with the assumptions regarding the costs of administration of bendamustine, namely £272 for the first administration, and £226 subsequently. These values are similar to those assumed for the administration of ofatumumab for CLL (£237 first administration, £220 subsequent administrations),[38] taken appropriately from the NHS Reference costs 2008-09.

Other costs while on treatment

All patients on active treatment are assumed to have one haematologist outpatient visit per 28-day treatment cycle. The cost per visit is £209 for all drugs except bendamustine, for which the cost is £131. The ERG agrees with these assumptions for drugs other than for bendamustine and has received advice that a frequency of one visit for each of the first two cycles in order to monitor the patient for adverse events is appropriate. Thereafter, the patient would have no further visits whilst on treatment. In addition, the ERG considers that the cost per visit for a bendamustine patient should be £270; i.e. the rate for day case attendance (equal to the submission's assumed cost for the first infusion of bendamustine), not the cost of £131. With these revised assumptions, the ICER decreases marginally from £12,000 to £11,900 per QALY.

5.2.6.2 Costs when not on treatment

Blood transfusions

The total cost per patient of blood transfusions is an important driver of cost-effectiveness of bendamustine. The ERG has received clinical advice which strongly disagrees with the assumption that patients in progressive disease will have a blood transfusion every three weeks. Given that patients are in progressive disease typically for about five to six years (Source: Napp Submission, Section 6.7.4, Table 6.2.6 p138), this implies that a patient receives an average of approximately 100 blood transfusions.

This suggests high mean discounted blood transfusion costs of £28,000 for bendamustine patients and £21,700 for chlorambucil patients. Instead, advice to the ERG suggests that patients typically receive a blood transfusion every four weeks for the last six months of their life and is likely to be the same in regardless of initial treatment. Therefore, ignoring discounting effects arising from different times to progression, the incremental cost of blood transfusions is zero, and the base case ICER falls substantially from £12,000 to £7,000 per QALY. Allowing for discounting, the ICER would be approximately £7,000 per QALY.

Given an assumption of equal cost of blood transfusions between treatment arms, the relevance of the cost per transfusion is much reduced. Nonetheless, for completeness, the ERG has addressed this issue briefly. The ERG agrees with the submission's assumption that each transfusion comprises two units of red blood cells at £261. However, the ERG disagrees with the assumption that the administration of a transfusion costs £85 (Source: Napp Submission, Section 6.5.6, Table 6.20, p123). Instead, the ERG favours a value of £272, representing the cost of a day case attendance (equal to Napp's assumption for the administration of the first infusion of bendamustine), given that a transfusion typically lasts four hours.

Cost of haematology outpatient follow up

The ERG agrees with a cost of £131 for a haematologist outpatient attendance, but disagrees with the frequency of visits likely to be required for patients in different disease states. Although the ERG's position is informed by fewer haematologists than provided information for the submission, it has explored a range of different assumptions for follow-up frequency as suggested by a clinical advisor.

The ERG agrees with the frequency of monthly follow up in stable disease. For people showing a partial response, the ERG suggests two monthly follow up would be more likely than the three monthly assumption in the submission. The ERG has been advised that follow up of patients in complete response is likely to be two monthly rather than the six monthly assumption in the submission. Finally, the ERG suggests that follow up for patients in progressive disease is likely to be less frequent than assumed in the submission: six weekly rather than three weekly.

Implementing the ERG's suggested frequencies of follow up in the submitted model gives an ICER for bendamustine of £11,500 per QALY.

5.2.6.3 Costs of treating adverse events

The ERG agrees with the modelled treatments for AEs used in the submitted model and reported in the table in Appendix A, page 99 of the submission.

5.2.7 Assessment of uncertainty

The submission includes appropriate modelling of the key parameters for the probabilistic sensitivity analysis using appropriate distributions.

5.3 Manufacturer's results

The results from the submitted model are shown in Table 17 below. See pages 148–158 of Napp's submission for further details. The base case ICER for bendamustine versus chlorambucil for first line treatment of CLL is £12,000 per QALY. Using completely independent, much simplified calculations, the ERG derive a similar ICER, of £8,600 per QALY (see Appendix C, page 118). Clearly, this is no substitute for the manufacturer's comprehensive model, but it is useful as an independent check and to help improve our understanding of the main drivers of the cost-effectiveness of bendamustine.

Treatment with bendamustine is predicted to yield a mean of 2.9 extra undiscounted life years, and 1.27 extra discounted QALYs compared to chlorambucil, of which 0.98 are gained in PFS and 0.29 in progressive disease. Treatment with bendamustine is expected to cost £15,200 more (discounted) per person than chlorambucil. This difference is largely explained by the greater costs associated with bendamustine in the following: per person acquisition cost compared to chlorambucil (+£4,600), first line drug administration (+£1,200), blood transfusion (+£6,300), and haematologist visits in progressive disease (+£2,400).

The per patient costs associated with acquisition, administration and monitoring of FC treatment, and treatment of AEs from first- and second line treatments are all low.

Table 17. Base case results of Napp's model (mean per patient, unless stated otherwise)

		Bendamustine	Chlorambucil	Bendamustine – Chlorambucil
PFS (years, undisc.)	Mean	2.1[†]	0.8[†]	1.3[†]
	Median	1.7	0.6	1.1
PD (years, undisc.)	Mean	7.8[†]	6.1[†]	1.7[†]
Life years (undisc.)	Mean	9.8[†]	6.9[†]	2.9[†]
	Median	8.3	5.8	2.5
QALYs (disc.)	PFS	1.52	0.54	0.98
	PD	3.30	3.01	0.29
	Total	**4.82**	**3.55**	**1.27**
First line drug cost (disc.)		£4,726	£150	£4,576
First line drug admin (disc.)		£2,922	£1,706	£1,216
Second line FC drug acquisition cost (disc.)		£437[†]	£332[†]	£105[†]
Second line FC admin & monitoring cost (disc.)		£343[†]	£260[†]	£83[†]
Adverse events first line (disc.)		£375	£190	£185
Adverse events second line (disc.)		£155	£117	£37
Blood transfusions (disc.)		£28,007[†]	£21,708[†]	£6,299[†]
Haematologist visits in PD (disc.)		£10,579[†]	£8,200[†]	£2,379[†]
Other costs (disc.) #		£1,456[†]	£1,158[†]	£299[†]
Total costs (disc.)		**£49,000**	**£33,821**	**£15,179**
ICERs				
Cost per life-year gained				£7,600[†]
Cost per QALY				**£12,000**
Probability bendamustine cost effective at WTP of		£20,000 / QALY		**90%**
		£30,000 / QALY		**98%**

[†] Calculated by the ERG; all other values taken from the submission
Comprises blood count and biochemistry in all health states when not on treatment and haematologist visits (SD, PR, CR, not PD) when not on treatment.

Numerous one-way sensitivity analyses are performed for the submission (Source: Napp Submission, Section 6.7.7, Table 6.31, pp140–142). In summary, it was found that the ICER is insensitive to:

- the statistical distribution for survival analysis (PFS and OS)

- the exclusion of the treatment covariate for PFS and OS

- the use of the upper or lower confidence intervals for response rates

- reasonable variations in FC efficacy

- reasonable variations in costs, except when health state costs when not on treatment (haematologist visits, blood transfusions, blood count, biochemistry) are omitted completely, in which case the ICER falls to £4,900 per QALY

- the source of utility data.

The ICER is largely insensitive to variations in the re-treatment algorithm, except when re-treatment with bendamustine is allowed, when it decreases to £8,700 per QALY.

The submission estimates the ICERs for the following subgroups of patients (Source: Napp Submission, Section 6.9.4, Tables 6.35, 6.36 and 6.37, p146–147):

- Patients age ≥ 65   ICER = £12,600 per QALY,

- WHO ≥ 1,   ICER = £13,500 per QALY,

- Patients age ≥ 65, and WHO ≥ 1   ICER = £13,600 per QALY.

5.4 Summary of uncertainties and issues

Overall, the ERG considers that the submitted model and report are of good quality.

Other cost-effectiveness models of bendamustine for CLL

Napp found no cost-effectiveness studies directly relevant to the appraisal of bendamustine for CLL (Section 5.1.1, p48). However, the ERG identified a recent conference poster presentation reporting a cost-effectiveness study of bendamustine versus alemtuzumab and chlorambucil for CLL.[25] This was presented at the ISPOR international meeting in 2010. Using a US payer-perspective, the ICER for bendamustine versus chlorambucil was $50,800 per QALY (approximately £33,000 per QALY). The submission base case ICER of £12,000 per QALY is substantially lower than this US study. This is largely explained by the fact that the US study predicts a far lower life expectancy on bendamustine (median overall survival 6.1 years for US study vs. 8.3 years for the submission), highlighting the influence of overall survival gains in determining the cost effectiveness of bendamustine.

Model structure

Broadly speaking, the structure of the submitted model is typical of many models in haematological malignancy, in that the health states PFS and PD are modelled (Section 5.1.3, p48).

ERG base case

We disagree with the following assumptions, which have important consequences for the cost-effectiveness of bendamustine:

- **Timings of blood transfusions**. We disagree with Napp's assumption that patients in PD have a blood transfusion every three weeks. Given that patients are in PD typically for about five to six years (Source: Napp Submission, Section 6.7.4, p138), this implies that a patient receives an average of approximately 100 blood transfusions. Instead, our clinical advisor states that patients typically receive a blood transfusion every four weeks for the last six months of their life for both treatment arms. Therefore, ignoring discounting, the incremental cost of blood transfusions is zero, and Napp's base case ICER falls substantially from £12,000 to £7,000 per QALY.

- **OS benefit of bendamustine vs. chlorambucil**. We believe that the modelled treatment effect in terms of the hazard ratio of overall survival is too high (Section 5.2.4, p76). Using the hazard ratio based on the most up to date data, Napp's base case ICER decreases slightly from £12,000 to £11,700 per QALY. Also, Napp's ICER of £7,000, adjusted for zero incremental blood transfusion costs, increases substantially, to £9,700 per QALY. In addition, when we use this updated hazard ratio, the model predicts that patients in the two treatment arms spend very similar times in PD. It could be argued that this is plausible, i.e. that bendamustine does not extend survival in PD compared to chlorambucil.

- **In addition,** the ERG disagrees with Napp's assumed dose intensities of bendamustine and chlorambucil and their assumed frequencies of visits to a haematologist when not treated. The ICER changes only slightly when these assumptions are revised.

Uncertainties in cost-effectiveness of bendamustine

In the RCT, a higher proportion of patients in the chlorambucil arm took expensive second line drugs compared to patients in the bendamustine arm (Section 5.2.2, p72). We are broadly satisfied with Napp's method of dealing with this issue, but we suggest that this introduces some uncertainty in to the estimation of the cost-effectiveness of bendamustine.

Given that OS from the RCT is immature, Napp are forced to extrapolate survival over many years. Whilst their extrapolation is reasonable, we caution that this introduces uncertainty to the modelled OS, and hence to the cost-effectiveness of bendamustine.

6 Additional 'exploratory' or other work undertaken by the ERG

6.1 Derivation of ERG base case ICER

Here, the impact of using alternative assumptions for items discussed in the earlier sections is quantified, both individually and in aggregate. An alternative ICER of £9,400 per QALY is estimated by updating the submitted model for the items where the ERG believes that alternative assumptions are more appropriate (Table 18). Changing the assumption regarding the frequency of blood transfusions has a marked effect on estimated cost effectiveness. When the OS hazard ratio is changed from 1.66 to 1.3, the base case ICER is virtually unchanged. However, if we first assume no incremental blood transfusion costs (first item in table), the reduction in the hazard ratio increases the ICER substantially (from £7,000 to £9,700 / QALY).

This section then considers scenario analyses applied separately to the submission base case and the ERG's proposed alternative base case (Table 18).

The ERG has not estimated alternative ICERs for the three subgroups presented in the submission by age and performance status. This is because updated estimates of the hazard ratios for OS in these subgroups have not been made available.

Table 18.   Derivation of alternative deterministic ICER for bendamustine vs. chlorambucil based on our proposed alternative assumptions

Item		ICER bendamustine vs. chlorambucil (£/QALY)
	Submission base case	**£12,000**
1 [a]	Blood transfusion costs equal both treatment arms	£7,000
2 [b]	OS hazard ratio from 1.66 to 1.3	£11,700
3 [a]	Frequencies of visits to haematologist when not treated	£11,500
4 [c]	Dose intensities 90% bendamustine, 95% chlorambucil	£11,600
	Alternative base case (combination of all items)	**£9,400**

[a] See Section 5.2.6, p81
[b] See Section 5.2.4, p76
[c] See Section 5.2.6, p81

Table 19. Important scenario analyses applied separately to Napp's base case versus proposed alternative base case

Item		Revised ICER from submission base case	Revised ICER from alternative base case
	Base case	**£12,000**	**£9,400**
1 [a]	Cost second line drugs received in RCT, model unadjusted OS from RCT	< £10,900	< £8,700
2 [a]	Cost no second line drugs, estimate OS assuming no second line drugs	< £10,900	< £8,700

[a] See Section 5.1.3, p72

7   Discussion

7.1   Summary of clinical effectiveness issues

- The literature search strategy carried out for the submission seeking RCTs and non-RCTs was appropriate, and replicable. Of note, however, is that the searches conducted for non-RCTs were not adequately translated. The Medline and Medline In-process search strategy was exactly replicated in Embase. Consequently, some of the search terms were not recognised. The manufacturer had also searched key word terms and the ERG re-ran the search applying the correct Emtree thesaurus terms, and conclude that while not good practice, that it was not a significant problem in the context of the submission. In addition, in some cases significant discrepancies in the resulting hits were noted these could have been accounted for given the search date and database/interface used. One additional review paper was found (Pinilla-Ibarz J, *Cancer Control* 2010 **17**(2 Suppl): 4–15), which was not considered in the discussion. However, the ERG conclude that it would not alter the discussion presented in the main submission. The ERG is confident that there are no relevant and good quality studies which have not been presented in the submission.

- The submission from Napp included one good quality RCT (Study 02CLLIII). However, as an open-label study it lacks blinding for both participants and investigators which introduces the potential for bias. Outcomes were, however, reviewed by an independent team according to criteria defined by the National Cancer Institute Working Group on CLL, and the response criteria had to be met for at least eight weeks in order for patients to be classified as complete or partial responders. Patients were classified as 'non-responders', if neither PR nor CR were confirmed or their tumour response was not evaluable. A patient had stable disease if CR, PR, and PD criteria were not met. Response was assessed after three treatment cycles and at the end of treatment.

- The maximum follow up was approximately five years. It should be noted that median survival is two to seven years in the population of interest. Therefore, a

longer follow-up may be required in trials of therapies for CLL to increase the validity of the results.

- In Study 02CLLIII, patients receiving bendamustine had a higher ORR than those in the chlorambucil group (68% vs 31%; P<0.0001). The median PFS was also significantly longer with bendamustine than with chlorambucil (21.6 months vs 8.3 months; P<0.0001). Survival analysis data in the main submission (35 months) show a non-statistically significant advantage for bendamustine (P=0.1623). The manufacturer also provided results from an updated trial analyses (with median observation time 54 months) which confirms that bendamustine offers significantly greater response rates and PFS, and a much longer time to next treatment than shown on chlorambucil. However, while this supports the analysis presented in the main submission 54 months remains a short duration over which to reach conclusions regarding OS benefits.

- Adverse events were reported for 89% of patients in the bendamustine group and 81% of the chlorambucil group, the most common being haematological. Severe infections of Grade 3 or 4 occurred in 8% and 3% of treated patients in the bendamustine and chlorambucil arm, respectively, with one Grade 4 infection in the chlorambucil arm. In general, these events are consistent with those expected in this patient group

- QoL data were collected only during the treatment period and therefore inadequate to capture the long term effects of bendamustine as opposed to chlorambucil.

7.2 Summary of cost effectiveness issues

Overall, the ERG believes that the submitted model and reporting are thorough and of good quality. Furthermore, the ERG found no logical errors in the model.

Broadly speaking, the structure of the submitted model is typical of models for agents in haematological malignancies, in that the main health states are progression free survival and progressive disease. However, the submitted model has a more sophisticated structure in two respects;

- PFS is split in to SD, PR and CR. The depth of response influences the utilities (better response, higher utility) and the disease-management costs (better response, lower cost).

- re-treatment with first line therapy and subsequent second line FC therapy is modelled.

The ERG believes that this structure is appropriate.

The submitted base case ICER for bendamustine vs. chlorambucil is **£12,000 per QALY**. When the ERG updates the submitted model using alternative assumptions regarding the timings of blood transfusions, the modelled overall survival hazard ratio, the dose intensities of bendamustine and chlorambucil and the assumed frequencies of visits to a haematologist when not treated, the ICER decreases slightly to **£9,400 per QALY**.

The submission estimates the cost-effectiveness of bendamustine for the following subgroups;

- Patients age ≥ 65,   ICER = £12,600 per QALY,

- WHO ≥ 1,   ICER = £13,500 per QALY,

- Patients age ≥ 65, and WHO ≥ 1,   ICER = £13,600 per QALY.

The ERG cannot check these ICERs because there is no independent source with which to check subgroup-specific response data and the subgroup-specific survival curves. Also, the ERG was prevented from deriving alternative ICERs for subgroups by lack of access to updated estimates of the hazard ratios for overall survival for subgroups.

Given that overall survival from the RCT is immature, Napp are forced to extrapolate survival over many years. Whilst their extrapolation is reasonable, we caution that this introduces uncertainty to the modelled overall survival, and hence to the cost-effectiveness of bendamustine.

In the RCT, a higher proportion of patients in the chlorambucil arm took expensive second line drugs compared to patients in the bendamustine arm. We are broadly satisfied with Napp's method of dealing with this issue, but we suggest that there are two

alternative methods. In the first method, when we cost all 2nd-line drugs received in each treatment arm in the RCT and model the actual, unadjusted overall survival from the RCT, Napp's base case ICER falls from £12,000 to <£10,900 per QALY, and our proposed base case ICER of £9,400 falls to < £8,700 per QALY. In the second method, when we do not cost the second line drugs received in the RCT, but estimate overall survival for each treatment arm assuming no second line drug treatment, the ICERs fall in the same way.

7.3   Implications for research

- Bendamustine:

    - continued follow-up relating to OS in Study 02CLLIII

    - Given that combination of agents is often used in haematology practice study of bendamustine in combination with other agents may be valuable

- As there is insufficient utility data to inform cost-effectiveness modelling there is a case for further study in this area

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9 APPENDIX A: Health economic model – adverse events costs

Adverse event	Treatment type	Treatment	% patients receiving treatment	Total unit cost	Total units (mg/appointments/ admission days)	Total cost per AE episode
Cytopenias - GCSF	i.v. infusion	Haematologist consultation	100%	£130.71	1.00	£817.09
	GCSF	Neulasta (Pegfilgrastin)	100%	£686.38	1.00	
Cytopenias - Erythropoietin	Erythropoietin	Erythropoietin treatment	100%	£1,188.61	1.00	£1,188.61
Nausea (Grade 1 or 2)	Anti emetics	Metoclopramide	50%	£0.004	87.5	£0.24
		Domperidone	50%	£0.002	70	
Nausea/vomiting (Grade 1 or 2)	Anti emetics	Metoclopramide	50%	£0.004	87.5	£0.24
		Domperidone	50%	£0.002	70	
Anaemia (Grade 3 or 4)	Transfusion	Blood transfusion	100%	£346.06	1	£453.12
	Consultation	Nurse	50%	£83.40	1	
		Consultant	50%	£130.71	1	
Pyrexia (Grade 3 or 4)	i.v. antibiotics	Tazocin	100%	£0.003	126000	£3,076.99
	Hospital care	Inpatient admission	100%	£2,652.23	1	
Pneumonia (Grade 3 or 4)	i.v. antibiotics	Tazocin	100%	£0.003	126000	£2,188.00
	Hospital care	Inpatient admission	100%	£1,763.24	1	
Diarrhoea (Grade 1 or 2)	Anti-diarrhoeal	Loperamide	50%	£0.018	21	£0.43
		Codeine	**50%**	**£0.002**	**270**	

Table reproduced from Napp submission, Table 6.21, p138

Drug prices taken from BNF 59, except erythropoietin cost which was from Wilson 2007

10 APPENDIX B: Napp responses to queries from PenTAG

Points for clarification

Detailed below are comments/points of clarification on the submission. Please note that all questions are priority questions.

Section A: Clarification on effectiveness data

A1. Please provide baseline information for the additional need-to-treat criteria specified (section 5.3.3, p43).

A breakdown of the number of patients meeting the need-to-treat criteria is shown on the next page.

Study and indication specific inclusion criteria

	Number (%) of patients					
	Bendamustine (n = 162)		Chlorambucil (n = 157)		Total (n = 319)	
Haemopoietic insufficiency with non-haemolysis-induced haemoglobin <10 g/dL	159	(98)	148	(94)	307	(96)
Thrombocytopenia <100 x 10^9/L	34	(21)	30	(19)	64	(20)
B symptoms	80	(49)	79	(50)	159	(50)
Persistent or recurrent pyrexia of unknown origin >38°C	15	(9)	27	(17)	42	(13)
Night sweats	74	(46)	75	(48)	149	(47)
Unexplained weight loss >10% weight loss in the last 6 months	44	(27)	39	(25)	83	(26)
Rapidly progressive disease	53	(33)	47	(30)	100	(31)
Risk of organ complications from bulky lymphomas	0	-	3	(2)	3	(<1)
Comment not classifiable – need to treat: increasing pleural effusion with B-CLL tumour cells	0	-	1	(<1)	1	(<1)
Comment not classifiable – need to treat: abdominal lymph node conglomerate may cut port arteria to kidney	1	(<1)	0	-	1	(<1)
Criteria not specified	1	(<1)	6	(4)	7	(2)

A2. Please clarify the median figures cited e.g. bendamustine, median 23.9 (TTP, ITT population) vs bendamustine, median 21.6 (PFS, ITT population): as TTP is more likely to happen we would expect the median figures for TTP to be lower than for PFS. (Figure 5.5, page 57 and Figure 5.7, page 60)

The definitions of progression-free survival (PFS) and time to progression (TTP) applied in the study were:

Progression-free survival (PFS)
The time from randomisation to first PD or relapse after inter-current remission or death for any cause.

Time to progression (TTP)
The time from randomisation to first PD or relapse after inter-current remission or CLL-related death.

The median times for PFS and TTP in the report are correct.

The reason median PFS was shorter than median TTP is because non CLL-related deaths were included with PFS (but not with TTP). Therefore median time until an event would have been shorter with PFS than with TTP.

A3. The figures cited in Table 5.8 for 'Time to onset of event' are incorrect, they are identical to the figures cited in Table 5.7 (PFS) on page 58. Please provide the correct figures (table 5.8, page 61).

Thank you for drawing this to our attention - you are correct that there was an error. The correct tables are included on the next page.

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Progression-free survival based on ICRA – Kaplan-Meier estimates (intention-to-treat population)

Analysis Statistic	Bendamustine		Chlorambucil		Hazard ratio (95% CI)[*] (chlorambucil/bendamustine)	P-value
All patients, n (%)	162		157		4.37 (3.14 – 6.07)	<0.0001
Patients with events	86	(53.1)	101	(64.3)		
Censored patients	76	(46.9)	56	(35.7)		
Quartiles (95% CI), months:						
25. percentile	13.1	(9.6 – 17.0)	5.6	(4.2 – 5.6)		
50. percentile	21.6	(18.6 – 31.0)	8.3	(5.9 – 11.3)		
75. percentile	40.4	(33.2 – NA)	14.0	(12.0 – 15.9)		
Time to onset of event:[†]						
12 months	78.6	(94)	34.9	(31)		
24 months	47.9	(54)	3.0	(2)		
36 months	30.9	(23)	1.5	(1)		
48 months	22.2	(7)	0.0	(0)		
54 months	17.8	(3)	0.0	(0)		

[*]Hazard ratios and their 95% confidence intervals are adjusted for Binet stage and based on the Cox regression proportional hazard model).
[†]Time to onset of event is summarized with Kaplan-Meier estimates and (number at risk)

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Overall survival – Kaplan-Meier estimates (intention-to-treat population)

A4.   Please provide details of the EORTC data from study 02CLLIII (section 5.5, p62). As these data total 60 pages, we have provided them as a separate pdf document.

Section B: Clarification on cost-effectiveness data

*B1. Please clarify the following: "The average dose applied in the chlorambucil group reached 95% of the planned dose whereas 90% was achieved in the bendamustine group". Are the 95% and 90% figures "dose intensities"? i.e. 95% = total dosage actually received over all chlorambucil patients over entire duration of the trial divided by total dosage over all chlorambucil patients over entire duration of the trial if all chlorambucil patients took their planned dose (0.8mg/kg on days 1 and 15 of 28 day cycle) <u>whilst in PFS</u> ? Expressed another way, in the model, the total average dose for patients on chlorambucil over the entire trial is 549mg (cell D12, worksheet "Costs"). If PenTAG's understanding of the 95% figure above is correct, then the average total dose of chlorambucil actually taken in the trial should be 549mg * 95% = 521mg. Similarly the average total dose for patients on bendamustine over the entire trial is quoted as 1,715mg (cell C12, worksheet "Costs"). If PenTAG's understanding of the 90% figure above is correct, then the average total dose should be 1,715mg * 90% = 1,544mg (page 80). If the 95% and 90% figures are not "dose intensities", please specify what these numbers represent?*

In the economic model, the cost of bendamustine and chlorambucil was based on the planned dose. As noted, this does not account for the fact that some patients did not receive the planned dose within each treatment cycle. The relative dose of the patient measures the extent to which patients received the planned dose. The formula applied to calculate the relative dose is presented below:

The exclusion of this relative dose was a simplifying modelling assumption, which was reasonable given patients received close to the planned dose (95% and 90%).

The base case model was rerun assuming that the relative dose (dose intensities) matched those seen in the trial, 95% for chlorambucil and 90% for bendamustine, rather than the planned doses. The results are as below:

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Model results with relative dose

	QALYs	Costs
Bendamustine	4.82	£48,527
Chlorambucil	3.55	£33,814
Bend. - Chlor.	1.27	£14,714
ICER (Bend. *vs.* Chlor.)	£11,594	

B2. If patients progress within the first three months they are out of the trial, please clarify how this is dealt with in the model (Section 6.3.1, Figure 6.1 (page 87) and Figure 6.2 (page 88) with reference to CSR, page 25).

Patients who progress within the first 3 months are not removed from the trial analyses completely; they continue to be followed up for overall survival and start of antineoplastic therapy.

These patients were included in the 02CLLIII analyses that inform post-progression parameters in the model i.e. the analysis of time to re-initiation of antineoplastic therapy and the overall survival analysis.

Following progression these patients are treated in the same way as patients who progress after a period of response (partial or complete) or stable disease.

B3. Please clarify the number of retreatment cycles permitted in the model before subsequent treatments are given (section 6.2, p88).

The total number of cycles were not limited but were determined by the probability of attaining a sufficient response to the previous course of therapy (>12 months) and the influence of competing events such as death (absorbing health state). The net effect of these led to 63.1% of chlorambucil patients receiving one or more retreatment cycles and the mean number of cycles for those patients who were retreated was 1.13.

B4. Please explain how mortality for patients in the best supportive care state is dealt with in the model (Section 6.3.1, Page 105, also Figure 6.1 (page 87) and Figure 6.2 (page 88)).

Mortality for patients receiving chlorambucil and bendamustine was modelled directly from the 02CLIII trial data using parametric survival analysis; it was not extrapolated from other surrogate endpoints such as response or progression. Endpoints such as response and progression were used solely to estimate costs and utilities for surviving patients. The model design was essentially that of a partitioned survival model. That is, overall survival was calculated independent of the health state through extrapolation of

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survival curves; which is in contrast to a standard Markov model where mortality rates are assigned to each health state. Partitioned survival models have been submitted to NICE in a number of recent technology appraisals.[‡]

This method explicitly links mortality rates to time in model rather than to specific health states. As mortality data are taken directly from the trial, the correlation between the distribution of patients across health states and the mortality rate at different points of time in the 02CLLIII trial will be captured. This method also ensures that the model predictions closely match the overall survival data observed in 02CLLIII.

B5. Please describe how background mortality; e.g. death from stroke, is dealt with in the model (Section 6.3.1, Figure 6.1 (page 87) and Figure 6.2 (page 88)).

As above, the mortality rate was estimated by extrapolating the overall survival data in the model by applying parametric techniques. Therefore, the 'background' mortality was the non CLL-related deaths present in the trial population. Of the 72 deaths reported in the trial, 13 patients in the bendamustine group and 21 patients in the chlorambucil group reported CLL deaths; conversely there were 18 non CLL-related deaths in the bendamustine group and 20 non CLL-related deaths in the chlorambucil group (including some patients with unknown cause). Note that only 65 death events are included in the parametric overall survival analysis (Bendamustine: 26; Chlorambucil: 39). This is because we excluded patients, who were not examined, from all the analyses for the economic model. The CLL deaths in this patient group are Bendamustine: 11; Chlorambucil: 20. Non-CLL deaths are Bendamustine: 12; Chlorambucil: 13 and unknown causes are Bendamustine: 3 and Chlorambucil: 6.

B6. Please explain the basis of 50% / 50% split between fludarabine + cyclophosphamide and best supportive care (BSC) (section 6.2, p88).

The 50%/50% split between treatment with fludarabine + cyclophosphamide and BSC was based on feedback from the advisory board as representing UK clinical practice. A full description of the advisory board can be found in Section 6.5.4 (Page 131) of the original report.
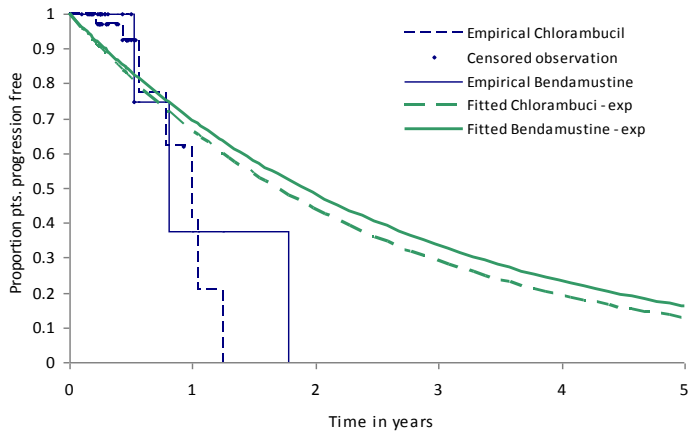
B7. In your submission it is stated 'To be conservative the log-logistic, which appears to provide the best fit by visual inspection, is therefore used'. Please provide us with plots for alternative survival functions and associated AIC data (section 6.3, p96).

The survival curves and AIC data are presented below.

Figure: Different parametric functions used for time to progression from stable disease

1. GlaxoSmithKline UK. Ofatumumab (Arzerra[®]) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab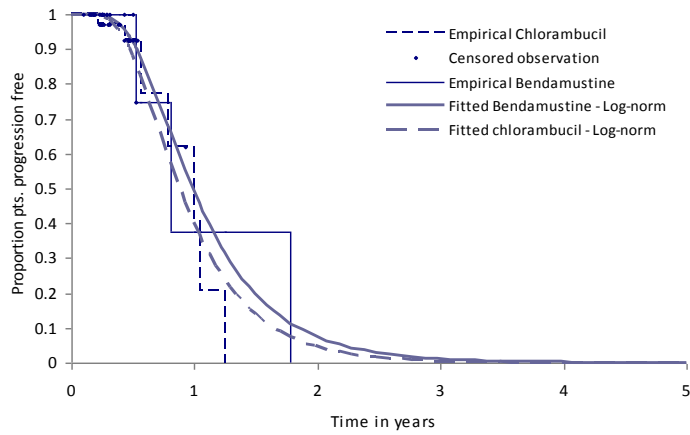. Manufacturer's NICE STA Submission 2010. Available from: http://www.nice.org.uk/nicemedia/live/12264/49445/49445.pdf (**see pages 91 - 93)**

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(a) Exponential

(b) Weibull

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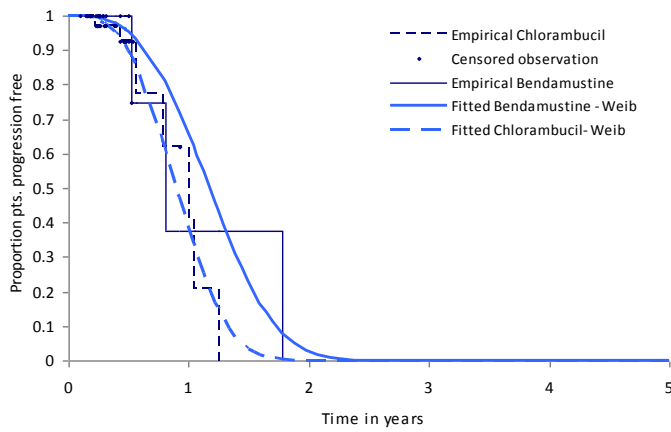
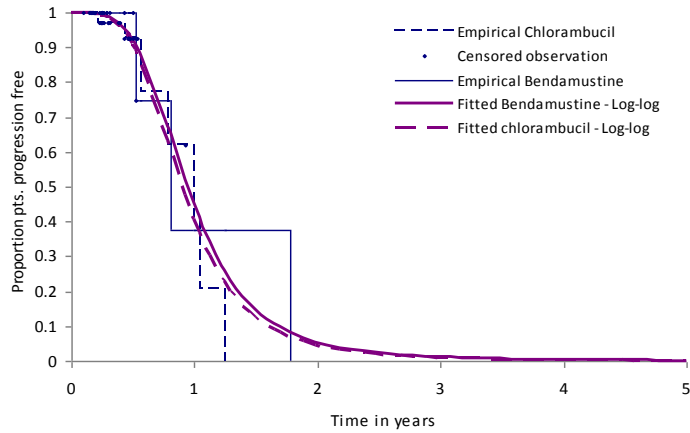### (c) Log-normal

(d) Log-logistic (base case)

Table: AIC for different parametric functions used for time to progression from stable disease

Distribution	AIC
Exponential	50.98
Weibull	32.28
Log-logistic	33.37
Log-normal	33.94

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B8. Please explain how utilities are handled in relation to the utilities from the general public (Kind et al, BMJ, 1998)? (Section 6.4.6, Pages 124-125 (Beusterien 2010)).

The utilities presented in Beusterein 2010 have been adjusted to reflect the utility derived by mapping from the EORTC QLQ C-30 data collected in 02CLLIII. This was achieved by assuming that the 02CLLIII baseline utility value could be used to represent the stable disease state. For example, this resulted in utility estimates for use in the model of 0.83 for complete response; 0.76 for partial response; 0.70 for stable disease and 0.60 for progressive disease (health states following first line treatment). The utility values should therefore reflect the age composition of the 02CLLIII patients at baseline. No further adjustments were made for cohort age.

B9. Please provide the health state descriptions for the utility study, Beusterien et al (section 6.4, p177).

Stable disease

Health State: ∗
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up.

Partial response

Health State: ϕ
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have improved with treatment. • Your swollen glands in your neck, armpits, or groin are smaller than they were before treatment. • Daily activities may take more effort than usual, and you feel a little fatigued (tired and weak). You may feel short of breath during normal activities. • Sometimes, you don't feel hungry or you feel full after eating a little. • You occasionally have trouble sleeping because of night sweats that wake you up.

Complete response

Health State: ♣
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have improved with treatment. • You do not have swollen glands in your neck, armpits, or groin. • Daily activities do not take more effort than usual, but you feel slightly fatigued (tired and weak). You do not feel short of breath during normal activities. • Your appetite is normal. • You do not have trouble sleeping because of night sweats.

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Progressive disease

Health State: ▲
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms are getting worse. • Your swollen glands in your neck, armpits, or groin are bigger and visible. They may be uncomfortable. • Daily activities require a lot of effort, and you are almost always fatigued (tired and weak). You feel short of breath during normal activities. • Almost always, you don't feel hungry or you feel full after eating a little. • Most of the time, you have trouble sleeping because of night sweats that wake you up.

No change plus grade I/II nausea

Health State: ♦
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up. • Once a month when you receive treatment, you experience nausea for 24-48 hours, during which time you don't feel like eating, and food may have a funny metallic taste. Most of the time, this can be relieved with medication.

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No change plus grade I/II nausea/vomiting

Health State: ∞
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up. • Once a month when you receive treatment, you experience nausea and vomiting for 24-48 hours, during which time you don't feel like eating, and food may have a funny metallic taste. Most of the time, this can be relieved with medication.

No change plus grade III/IV anaemia

Health State:
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • You experience substantial fatigue (tiredness/weakness), and your ability to exercise (walking or shopping, etc.) is substantially limited. You feel short of breath during normal activities. You receive a 6-hour blood transfusion at the clinic, which relieves the fatigue for 2-3 weeks. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up.

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No change plus grade III/IV pyrexia

Health State: Ω
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up. • Once a month, you develop a fever due to infection, and this requires treatment in the hospital for 4 to 5 days.

Second-line treatment

Health State: ◘
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • This is your second time on treatment because your symptoms worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities require quite a bit of effort, and you are fatigued (tired and weak) much of the time. You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up.

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No change plus grade III/IV pneumonia

Health State
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up. • Once a month, you have pneumonia, which causes coughing, chest pain, fever, and breathlessness. This requires you to stay in the hospital for 7-10 days and receive intravenous antibiotics.

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No change plus grade I/II diarrhoea

Health State: ●
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • Your symptoms have stabilized with treatment. Your symptoms have not improved or worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities take more effort than usual, and you often are fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up. • Once a month when you receive treatment, you experience 3 to 4 episodes per day of diarrhoea (watery stools) that lasts for 3 to 4 days.

Third-line treatment

Health State: ♠
• You have cancer of the blood that may not be life-threatening, but it may affect your well-being. This disease results in a weakened immune system, increasing the chance of getting infections. • This is your third time on treatment because your symptoms worsened. • You have swollen glands in your neck, armpits, or groin that look like lumps and may be visible and uncomfortable. • Daily activities require a lot of effort, and you are almost always fatigued (tired and weak). You feel short of breath during normal activities. • Much of the time, you don't feel hungry or you feel full after eating a little. • You often have trouble sleeping because of night sweats that wake you up.

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Full health

Health State: §
 • You are in full health • You have no medical conditions; you are considered healthy

Dead

Health State: ♫
 • You are dead

Additional questions received from NICE via email correspondence

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1. Please could you provide an accessible reference source for the price of bendamustine cited in the submission (see Table 6.19, page 133). Within the submission the reference is: British National Formulary 59 available from http://www.medicinescomplete.com/mc/bnf/current but the ERG are not able to access this reference without paying for a subscription, and the information isn't in the BNF 59.

Bendamustine has only recently launched therefore it is still waiting to be included in external sources such as MIMS and BNF.

The closest we have to a formal source for the bendamustine price is an internal Trade Price List (September 2010), which includes the price of all Napp products. We hope this is sufficient for now. We have attached this document to the email.

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11 APPENDIX C: Simplified analysis of cost-effectiveness of bendamustine

In this section, we try to re-create the manufacturer's base case ICER of £12,000 per QALY using much simplified calculations. Clearly, this is no substitute for the manufacturer's comprehensive model, but it is useful as an independent check and to help improve our understanding of the main drivers of the cost-effectiveness of bendamustine.

Incremental total QALYs

First, we estimate the incremental total QALYs as:

(Mean discounted PFS bendamustine) x (mean utility in PFS bendamustine)

– (Mean discounted PFS chlorambucil) x (mean utility in PFS chlorambucil)

+ (Mean discounted PD bendamustine) x (mean utility in PD bendamustine)

– (Mean discounted PD chlorambucil) x (mean utility in PD chlorambucil)

= 1.96 x 0.78 – 0.75 x 0.74 + 5.86 x 0.67 – 5.08 x 0.67

= 1.51

Here, we estimate the mean utility in PFS for bendamustine = (response rate SD x utility SD + response rate PR x utility PR + response rate CR x utility CR) / (sum of response rates for SD, PR, CR) = (16% x 0.70 + 29% x 0.76 + 45% x 0.83) / (16% + 29% + 45%) = 0.78, and similarly mean utility in PFS for chlorambucil = 0.74. Also, we estimate the mean utility in PD for bendamustine and chlorambucil very approximately as the average of all the utilities for the PD health states = 0.67.

Our estimated incremental total QALYs of 1.51 is fairly close to 1.27 from the manufacturer's model. We believe that the difference is explained by the fact that we have a very broad approximation for the mean utility in PD.

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Incremental total costs

Next, we estimate the incremental total costs as:

Mean undiscounted bendamustine acquisition cost

+ Mean undiscounted bendamustine administration cost

– Mean undiscounted chlorambucil administration cost

+ Mean discounted FC acquisition and administration cost bendamustine arm

– Mean discounted FC acquisition and administration cost chlorambucil arm

+ Mean discounted bendamustine haematologist costs in PD

+ Mean discounted chlorambucil haematologist costs in PD

+ Mean discounted bendamustine blood transfusion costs

– Mean discounted chlorambucil blood transfusion costs

We ignore the acquisition cost of chlorambucil, the costs of treating AEs, the costs of blood counts and biochemistry because they are very low. We also ignore the costs of haematologist visits in PFS because patients stay in PFS for much less time than in PD. Also, for simplicity, we consider undiscounted costs for the first three quantities because they are incurred early.

- Mean undiscounted bendamustine acquisition cost = total dose (mg) over 4.9 cycles x price per mg

  Bendamustine is given at 100mg/m^{-2}, at a mean body surface area of 1.72m^2, which gives a mean of 172 mg. Given that bendamustine is given in minimum doses of 25 mg, we round up the dose to 175 mg per patient (as do the manufacturer). Hence the total dose per person for 4.9 cycles = 175 mg x 2 doses per cycle * 4.9 cycles = 1715mg. Bendamustine costs £2.76 per mg. Therefore the mean undiscounted bendamustine acquisition cost = 1,715 mg x £2.76/mg = £4,742.

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This is very close to the manufacturer's discounted cost of £4,726.

- Mean undiscounted bendamustine administration cost

  = undiscounted cost bendamustine administration first cycle + undiscounted cost bendamustine administration remaining 3.9 cycles

  = (cost one haematologist visit + cost first administration + cost second administration)

  + (cost one haematologist visit + two administrations per cycle x cost of subsequent administrations) x 3.9 cycles

  = (£132 + £272 + £227)

  + (£132 + 2 x £227) x 3.9

  = £630 + £2,279 = £2,909

  This is very close to the manufacturer's discounted cost of £2,922.

- Mean undiscounted chlorambucil administration cost

  = Mean undiscounted chlorambucil administration cost first treatment course + Mean undiscounted chlorambucil administration cost re-treatment course

  Mean undiscounted chlorambucil administration cost first treatment course

  = (Mean undiscounted chlorambucil administration cost per cycle) x(mean number of cycles)

  = £209 x 4.9 = £1,024.

  Next, given that patients on chlorambucil are re-treated on progression only if they do not progress in the first year;

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Mean undiscounted chlorambucil administration cost re-treatment course = (chlorambucil PFS at one year) x (mean undiscounted chlorambucil administration cost first treatment course)

= 0.312 x £1,024 = £319

Therefore:

Mean undiscounted chlorambucil administration cost = £1,024 + £319 = £1,343.

This is rather lower than the manufacturer's discounted cost of £1,706.

- Mean discounted FC acquisition and administration cost bendamustine arm

= Undiscounted cost per patient of a course of FC (acquisition + OP visit) x probability of receiving FC x discount factor

Undiscounted cost per patient of fludarabine acquisition

= total dose (mg) over 4.6 cycles x price per mg

Fludarabine is given at 25mg/m^{-2}, at a mean body surface area of 1.72m^2, which gives a mean of 43 mg. Given that fludarabine is given in minimum doses of 10mg, we round the dose up to 50 mg per patient (as do the manufacturer). Hence the total dose per person for 4.6 cycles = 50 mg x 3 doses per cycle * 4.6 cycles = 690 mg. Fludarabine costs £1.79 per mg. Therefore the mean undiscounted fludarabine acquisition cost = 690 mg X £1.79/mg = £1,233. We ignore the cost of cyclophosphamide because it is very low.

The administration cost of FC is £209 per cycle, which gives £209 x 4.6 = £961 over 4.6 cycles.

Hence, mean undiscounted FC acquisition and administration cost per course = £1,233 + £961 = £2,194.

Next, the probability that a patient receives FC equals 50% (half of patients receive FC on progression) x probability patient reaches PD. Given that patients

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in the bendamustine arm spend an average of 2.1 years in PFS, and the probability that a bendamustine patient is still alive after 2.1 years is 0.91;

Mean discounted FC acquisition and administration cost bendamustine arm

= Undiscounted cost per patient of a course of FC (acquisition + OP visit) X probability of receiving FC x discount factor bendamustine arm

= £2,194 x 50% x 0.91 / (1.035)^(2.1)

= £929

This is quite close to the manufacturer's discounted cost of £780.

- Mean discounted FC acquisition and administration cost chlorambucil arm equals (similarly):

= Undiscounted cost per patient of a course of FC (acquisition + OP visit) x probability of receiving FC chlorambucil arm x discount factor chlorambucil arm

Given that patients in the chlorambucil arm spend an average of 0.8 years in PFS, and the probability that a chlorambucil patient is still alive after 0.8 years is 0.96, and that only chlorambucil patients who progress within 12 months can receive FC;

Mean discounted FC acquisition and administration cost chlorambucil arm

= £2,194 x 50% x 0.96 / (1.035)^(0.8) x (1 - 0.312)

= £705

This is quite close to the manufacturer's discounted cost of £592.

- Mean discounted bendamustine haematologist costs in PD

(mean cost per haematologist visit) X (number of visits per year in PD) X (mean discounted years in PD bendamustine arm)

= £131 x (52/3) x 5.86

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= £13,306

Where the manufacturer assume one haematologist visit every three weeks whilst in PD.

This is larger than £10,579 in the manufacturer's base case, we believe because we have overestimated the time in PD as equal to OS – PFS. Instead, during some of this period, patients will have a response to FC treatment.

- Mean discounted chlorambucil haematologist costs in PD

(mean cost per haematologist visit) x (number of visits per year in PD) x (mean discounted years in PD chlorambucil arm)

= £131 x (52/3) x 5.08

= £11,535

This is larger than £8,200 in the manufacturer's base case, again we believe because we have overestimated the time in PD as equal to OS – PFS. Instead, during some of this period, patients will have a response to FC treatment or re-treatment with chlorambucil.

- Mean discounted bendamustine blood transfusion costs

= (mean cost blood + cost administration of one transfusion) x number of transfusions per year x mean discounted years in PD bendamustine arm

= (£261 + £85) x (52/3) x 5.86

= £35,144.

Where the manufacturer's assumption is for one transfusion every three weeks whilst in PD.

This is rather higher than the manufacturer's value of £28,007, we believe for the same reason as in the previous two bullet points.

- Mean discounted chlorambucil blood transfusion costs

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= (mean cost blood + cost administration of 1 transfusion) X number of transfusions per year X mean discounted years in PD chlorambucil arm

= (£261 + £85) X (52/3) X 5.08

= £30,466

This is rather higher than the manufacturer's value of £21,708, we believe for the same reason as in the previous two bullet points.

Costs

Combining all costs above:

Incremental total costs = £4,742 + £2,909 - £1,343 + £929 - £705 + £13,306 - £11,535 + £35,144 – £30,466

= £12,981

This is close to the manufacturer's figure of £15,179.

Estimated ICER

Hence the estimated ICER is £12,981 / 1.51 = £8,600 per QALY.

Given that this is close to the manufacturer's base case ICER of £12,000 per QALY, this gives us extra confidence in the accuracy of their ICER.