

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Ofatumumab in combination with
chlorambucil or bendamustine for
untreated chronic lymphocytic leukaemia**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ofatumumab in the NHS in England. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ofatumumab in the NHS in England.

For further details, see the [Guides to the technology appraisal process](#).

The key dates for this appraisal are:

Closing date for comments: 5pm on 25 November 2014

Second Appraisal Committee meeting: 21 January 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

- 1.1 Ofatumumab in combination with chlorambucil is recommended as an option for untreated chronic lymphocytic leukaemia only if:

- the person is ineligible for fludarabine-based therapy **and**
- bendamustine is not suitable **and**
- the company provides ofatumumab with the discount agreed in the patient access scheme.

1.2 People currently having treatment initiated within the NHS with ofatumumab that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Ofatumumab (Arzerra, GlaxoSmithKline) is a fully human, monoclonal antibody that is targeted against the CD20 cell surface antigen of B-lymphocytes and causes cell death. It is administered by intravenous infusion. Ofatumumab in combination with chlorambucil or bendamustine has a marketing authorisation in the UK for treating chronic lymphocytic leukaemia in people who have not had prior therapy and who are not eligible for fludarabine-based therapy.

2.2 The summary of product characteristics lists the following adverse reactions for ofatumumab, alone or with an alkylating agent, as affecting more than 10% of patients: upper and lower respiratory tract infections, neutropenia, anaemia, nausea, rash and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dose and schedule in the summary of product characteristics is 300 mg on day 1 followed by 1000 mg on day 8 (cycle 1), followed by 1000 mg on day 1 of subsequent cycles, for a minimum of 3 cycles, until best response or a maximum of 12 cycles (every 28 days). Best response is defined as a clinical

response that did not improve after 3 additional cycles of treatment. Ofatumumab is priced at £182 for a 100-mg vial and £1820 for a 1000-mg vial (British national formulary 66, 2014). Assuming 6 cycles and no drug wastage, the mean cost of a treatment course for ofatumumab is £11,466 for 6300 mg. The company has agreed a patient access scheme with the Department of Health that makes ofatumumab available with a discount. The size of the discount is commercial in confidence (see section 5.3). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by GlaxoSmithKline and a review of this submission by the Evidence Review Group (ERG; section 9).

Overview of the clinical trials

3.1 The company's systematic review identified 1 randomised controlled trial and 1 non-randomised clinical trial that provided evidence for ofatumumab for previously untreated chronic lymphocytic leukaemia:

- COMPLEMENT 1 was a phase III randomised controlled trial that evaluated ofatumumab plus chlorambucil compared with chlorambucil alone.
- OMB115991 was a phase II open-label, single-arm trial of ofatumumab plus bendamustine.

COMPLEMENT 1

3.2 COMPLEMENT 1 enrolled adults with previously untreated chronic lymphocytic leukaemia who were considered inappropriate for fludarabine-based therapy for reasons that included, but were not

limited to, advanced age or presence of comorbidities, and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. Overall, the investigators considered fludarabine-based therapy to be inappropriate for 92% of the patients enrolled: 158 were recruited before a change to the trial's protocol which specified that patients must be considered fludarabine inappropriate. Eligible patients were stratified by age (under 65 years and 65 years or over), disease stage (Binet A, B and C) and ECOG performance status (0–1 and 2). Patients were randomised to have ofatumumab plus chlorambucil (n=221) or chlorambucil alone (n=226) for a minimum of 3 cycles, until best response or up to a maximum of 12 cycles. Ofatumumab was administered as an intravenous infusion of 300 mg on day 1 and 1000 mg on day 8 during the first cycle, then 1000 mg on day 1 every 28 days for subsequent cycles. Chlorambucil was orally administered at 10 mg/m² on days 1–7 every 28 days).

- 3.3 The primary outcome was progression-free survival assessed by an independent review committee. Other efficacy outcomes were overall response rate, overall survival, prognostic and biological marker correlation with clinical response, time to response, duration of response and patient-reported outcomes. The Global Health Scale domain from the EORTC QLQ-C30 and Fatigue Scale from the EORTC, and the Quality of Life Questionnaire Chronic Lymphocytic Leukaemia 16-item module were pre-specified as the principal quality-of-life outcomes. Other patient-reported outcome instruments included the EuroQoL Five-Dimension (EQ-5D). Safety outcomes were adverse events (any grade), adverse events at grade 3 or higher, serious adverse events and death. Follow-up was every 3 months for up to 5 years. The intention-to-treat population was the primary population used for all efficacy assessments. The safety population was used for all safety

assessments and included patients who had at least 1 dose of a study drug.

OMB115991

- 3.4 OMB115991 enrolled patients with chronic lymphocytic leukaemia for whom the investigator considered fludarabine-based therapy to be inappropriate, and whose disease was previously untreated (n=44) or had relapsed (n=53). Patients had up to 6 monthly intravenous infusions of ofatumumab (cycle 1: 300 mg on day 1 and 1000 mg on day 8; subsequent cycles 1000 mg on day 1 every 28 days) in combination with up to 6 cycles of intravenous infusions of bendamustine (90 mg/m², days 1 and 2 every 28 days).
- 3.5 The primary outcome was overall response rate. Secondary outcomes included investigator-assessed progression-free survival, correlation of clinical and biological prognostic markers with clinical response, overall survival and minimum residual disease. Assessments to determine patient response or disease progression were performed at every 3-month follow-up visit until disease progression or until a maximum of 3 years. The company's submission included results of the primary outcome analysis for the previously untreated population. The clinical cut-off date for the primary end point analysis (28 February 2013) was after the last scheduled 3-month follow-up visit. The study will complete after the last patient withdraws from the study or completes follow-up.

Clinical trial results

COMPLEMENT 1

- 3.6 A total of 447 patients were randomised in 16 countries, of whom 80% (n=357) were enrolled in Europe. Median follow-up at the time of data cut-off was approximately 29 months. Across both arms of the study, around a third of patients (n=138) had discontinued

treatment per protocol, most commonly because of adverse events (n=66). Less than 20% of patients had died (n=74) and less than 15% withdrew from the study (n=55). Most patients had 6 or more cycles (ofatumumab plus chlorambucil 82%; chlorambucil 70%), with approximately two-thirds of patients stopping treatment after 6 cycles. Median overall exposure with a median number of 6 cycles was 6300 mg.

- 3.7 COMPLEMENT 1 met its primary end point of significantly prolonging progression-free survival in patients with previously untreated chronic lymphocytic leukaemia who were considered inappropriate for fludarabine-based therapy. Median progression-free survival, as assessed by the independent review committee, was 22.4 months for patients treated with ofatumumab plus chlorambucil, compared with 13.1 months for those having chlorambucil alone (hazard ratio 0.57 [95% confidence interval 0.45 to 0.72], $p < 0.001$). Risk of progression with ofatumumab plus chlorambucil was statistically significantly lower than with chlorambucil alone in all pre-specified sensitivity analyses (hazard ratios ranged from 0.52 to 0.61; all $p < 0.001$).
- 3.8 The company presented a range of Forest plots showing subgroup analyses of progression-free survival according to demographic and baseline characteristics, baseline fitness and comorbid condition burden, and prognostic factors. The results generally favoured ofatumumab plus chlorambucil rather than chlorambucil alone, but the differences were not always statistically significant.
- 3.9 The overall response rate with ofatumumab plus chlorambucil was significantly higher than with chlorambucil alone, as assessed by an independent review committee (82% and 69% respectively, $p = 0.001$). There was a higher rate of complete response with ofatumumab plus chlorambucil than with chlorambucil alone (12%

compared with 1%), but partial response was the same in both treatment groups (67%).

- 3.10 With a median follow-up of 28.9 months, median overall survival was not reached in either treatment group. There were 34 deaths (15%) in the ofatumumab plus chlorambucil group compared with 40 deaths (18%) in the group having chlorambucil alone (hazard ratio 0.91 [95% confidence interval 0.57 to 1.43], $p=0.666$). The company also reported survival rates for ofatumumab plus chlorambucil compared with those for chlorambucil alone at 2 years (89% and 87% respectively) and at 3 years (85% and 83% respectively).
- 3.11 Patients having ofatumumab plus chlorambucil had a significant longer median time to next treatment than those having chlorambucil alone (39.8 months compared with 24.7 months; hazard ratio 0.49 [95% confidence interval 0.36 to 0.67], $p<0.001$). With a median 6 months of treatment in both groups, this produced a median treatment-free period of approximately 34 months with ofatumumab plus chlorambucil and 19 months with chlorambucil alone.
- 3.12 Over a median of 6 treatment cycles, 428 patients completed at least 1 patient-reported outcome assessment. During treatment and follow-up:
- Patients in both treatment groups had numerically positive changes in Global Health Scale in the EORTC QLQ-C30, but these were not statistically significantly different from baseline values.
 - Similarly, patients in both groups had less fatigue from baseline according to the Fatigue Scale in the EORTC QLQ-CLL16, but there were no statistically significant changes from baseline.

- There were no statistically significant differences in EQ-5D scores between the 2 treatment arms.

The company concluded that this showed adding ofatumumab to chlorambucil did not negatively affect health-related quality of life.

OMB115991

3.13 Most patients (n=39, 89%) had all 6 cycles of study treatment. At the time of the primary end point analysis, the median duration of study was approximately 8.5 months and all 44 patients entered the follow-up phase. In the patients with previously untreated disease who had all 6 cycles of study treatment, ofatumumab plus bendamustine produced an overall response rate of 97%. Around half (n=19, 49%) had a complete response and a further 5% (n=2) had a complete response with incomplete bone marrow recovery. In 16 patients who were believed to have had a complete response, 9 tested negative for minimal residual disease.

Adverse effects of treatment

3.14 Safety data were based mainly on ofatumumab plus chlorambucil (COMPLEMENT 1), but included some additional data for ofatumumab plus bendamustine (OMB115991). Most patients in COMPLEMENT 1 had 1 or more adverse events during the study; 84% of patients (n=217) having ofatumumab plus chlorambucil had a treatment-related adverse event, compared with 65% (n=227) having chlorambucil alone. A higher proportion of patients in the ofatumumab plus chlorambucil arm had adverse events that were grade 3 or above compared with those having chlorambucil alone (60% compared with 45%). Adverse events leading to dose delays attributed to either ofatumumab or chlorambucil were reported more frequently in patients having ofatumumab plus chlorambucil

than in patients having chlorambucil alone (69% compared with 28%). However, a similar proportion of patients in each arm stopped study treatment because of an adverse event (13% ofatumumab plus chlorambucil; 14% chlorambucil alone).

- 3.15 The most common adverse events reported by at least 5% of patients in either treatment arm were neutropenia, rash, nausea and pyrexia. Those more common in the ofatumumab plus chlorambucil arm than in the chlorambucil alone arm were: neutropenia (27% compared with 18%), rash (25% compared with 10%) and pyrexia (21% compared with 10%). The incidence of nausea was similar in the 2 treatment arms (21% compared with 25% respectively).

Indirect treatment comparisons

- 3.16 The company explained that it was unable to conduct an anchored indirect treatment comparison using ofatumumab and bendamustine because the evidence for the combination was from a single-arm phase II study.
- 3.17 The company's systematic review identified 2 relevant studies that could form an evidence network for an adjusted indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil in patients for whom fludarabine is inappropriate, via the common comparator of chlorambucil. These studies were:
- COMPLEMENT 1: a phase III randomised controlled trial comparing ofatumumab plus chlorambucil with chlorambucil alone.
 - CLL11: a phase III 3-arm randomised controlled trial comparing rituximab plus chlorambucil, obinutuzumab plus chlorambucil, and chlorambucil alone.

3.18 Although an indirect comparison of ofatumumab plus chlorambucil and rituximab plus chlorambucil was feasible, the company considered it to be inappropriate because of limitations in the trial network and heterogeneity between COMPLEMENT 1 and CLL11. The company highlighted the differences between the 2 trials in terms of:

- chlorambucil dosage (the estimated dosage was 120 mg per cycle in COMPLEMENT 1 and 70 mg per cycle in CLL11)
- median cumulative dose of chlorambucil (728 mg in COMPLEMENT 1 and 384 mg in CLL11)
- duration of chlorambucil treatment (the planned number of cycles was 3–12 in COMPLEMENT 1 and 6 in CLL11, but there was a median of 6 cycles administered in each trial)
- patient populations (because of how fludarabine ineligibility was determined and the inclusion and exclusion criteria for the trials)
- how and when end points were assessed, and median duration of follow-up
- the results with chlorambucil alone.

3.19 The company's systematic review also identified 1 relevant study that could potentially inform an adjusted indirect comparison between ofatumumab plus chlorambucil and bendamustine, through a common chlorambucil comparator arm. This study, 02CLLIII, compared bendamustine with chlorambucil, but the company asserted that a robust, anchored indirect treatment comparison could not be performed because of a number of differences between this study and COMPLEMENT 1. It stated that the patient populations were not comparable because it considered the patients in 02CLLIII to be younger, physically fitter and more able to tolerate bendamustine. It also observed differences in chlorambucil dosage (planned dose was 112 mg per cycle in

02CLLIII and 120 mg per cycle in COMPLEMENT 1), how response rate and disease progression had been assessed, and marked differences between the efficacy results in the chlorambucil treatment arms.

3.20 The company said it was unable to perform an adjusted indirect comparison between ofatumumab plus chlorambucil and rituximab plus bendamustine. It explained that only interim results were available from the MaBLLe study, which investigated rituximab plus chlorambucil compared with rituximab plus bendamustine in fludarabine-ineligible patients. Moreover, the study included some patients with relapsed disease, did not have progression-free survival as its primary end point, and lacked a common chlorambucil alone arm.

3.21 The company concluded that the limitations of the trial network meant it was not possible to compare direct and indirect estimates, or to observe heterogeneity of treatment effect estimates, for comparisons of ofatumumab plus chlorambucil with rituximab plus chlorambucil, bendamustine, and bendamustine plus rituximab.

ERG comments

3.22 The ERG believed that the company's submission contained all relevant studies, but noted that neither the company's decision problem nor the single included randomised controlled trial (COMPLEMENT 1) addressed several comparators in the scope (chlorambucil plus rituximab, and bendamustine alone or plus rituximab). It also noted that the submission stated that the primary data sources for COMPLEMENT 1 and OMB115991 were the clinical trial reports, and that the studies had been published only as meeting abstracts and not as peer-reviewed publications.

3.23 The ERG commented that COMPLEMENT 1 was an open-label study and therefore lacked blinding, increasing the risk of bias. However, it noted that the primary end point, progression-free survival, was assessed by an independent review committee. The ERG noted that although inappropriateness of fludarabine-based treatment was added as an inclusion criterion after starting recruitment, post-hoc analyses showed that this was unlikely to have changed the findings of the study. The ERG concluded that the COMPLEMENT 1 trial population was generally reflective of patients likely to have the treatment in clinical practice in England, noting that the chlorambucil dosage in the study was the same as that used in clinical practice (10 mg/m² on days 1–7 for each 28-day cycle). The ERG agreed that the adverse-event profile reported in the company's submission was generally consistent with that expected for regimens including an anti-CD20 monoclonal antibody.

3.24 The ERG believed that none of the reasons cited by the company was sufficient to render an indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil invalid or irrelevant:

- Although the company stated that the use of rituximab plus chlorambucil in the relevant patient population is low, the ERG found that the estimated use of rituximab varied according to different sources, including clinical experts and professional organisations, with some saying that it is widely used. The ERG observed that rituximab had been included as a comparator in the final NICE scope.
- Despite the company claiming that there were important differences in trial design between CLL11 and COMPLEMENT 1 (see section 3.18), the ERG received clinical expert advice that

the patients in both trials were a good match to those unsuited to fludarabine in clinical practice. Furthermore, it was advised that there were no differences between the 2 populations that were likely to substantially affect the relative treatment effects. The ERG found only 1 baseline characteristic, the level of beta 2-microglobulin, that differed substantially between trials.

- The ERG was not convinced by the company's argument that a dose–response relationship had been shown for chlorambucil

The ERG agreed with the company that the validity of the indirect comparison was reliant on the reported trial characteristics. It also agreed that it was not possible to observe heterogeneity of treatment effect estimates within a comparison because of the limited number of studies.

3.25 The ERG performed an adjusted indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil using data from CLL11 and COMPLEMENT 1. It adjusted the progression-free survival hazard ratio between rituximab plus chlorambucil and chlorambucil alone, and that between ofatumumab plus chlorambucil and chlorambucil alone for beta 2-microglobulin and other variables that differed between CLL11 and COMPLEMENT 1:

- The ERG noted that in CLL11, progression-free survival was 16.3 months with rituximab plus chlorambucil and 11.1 months with chlorambucil alone. The hazard ratio for all patients for rituximab plus chlorambucil compared with chlorambucil alone was 0.44 (95% confidence interval 0.34 to 0.57). The progression-free survival hazard ratio for all patients in COMPLEMENT 1 for ofatumumab plus chlorambucil compared with chlorambucil was 0.57 (95% confidence interval 0.45 to 0.72).

- Using patient baseline characteristics from COMPLEMENT 1, the hazard ratio for progression-free survival for rituximab plus chlorambucil compared with ofatumumab plus chlorambucil was 0.96 (that is, rituximab plus chlorambucil was marginally more effective). Because the hazard ratio was close to 1, and given the uncertainties in undertaking an indirect comparison, the ERG assumed a progression-free survival hazard ratio of 1 for rituximab plus chlorambucil compared with ofatumumab plus chlorambucil. The ERG used this hazard ratio of 1 in the base case of its exploratory analyses.
- Using patient baseline characteristics from CLL11, the ERG estimated the hazard ratio for rituximab plus chlorambucil compared with ofatumumab plus chlorambucil to be 0.70. It used this in an exploratory sensitivity analysis.

3.26 The ERG also assumed that the 2 treatment regimens produced a disease response in an equal proportion of patients, because of both the assumption of equal progression-free survival distribution (with an adjusted hazard ratio) and a lack of data to adjust the response rates according to patient baseline characteristics. Estimated unadjusted response rates for rituximab plus chlorambucil as if it had been a treatment in COMPLEMENT 1 were as follows:

- Based on the independent review committee assessment (because this was used by the company in its base-case analysis), the overall response rate was 90% (complete response 10% and partial response 80%).
- Based on investigator assessment, the overall response rate was 95% (complete response 11% and partial response 84%).

- 3.27 The ERG performed an indirect comparison for overall survival, noting that the data were very immature (that is, there had been relatively few deaths during the limited follow-up period). Because of a lack of data, it was unable to adjust the overall survival hazard ratio of rituximab plus chlorambucil for differences in patient baseline characteristics between COMPLEMENT 1 and CLL11. In the base case for its exploratory analyses, the ERG assumed equal overall survival for ofatumumab plus chlorambucil and rituximab plus chlorambucil. Using an unadjusted indirect comparison, the ERG estimated the hazard ratio for rituximab plus chlorambucil compared with ofatumumab plus chlorambucil to be 0.73 (95% confidence interval 0.36 to 1.46) and used this in a sensitivity analysis.
- 3.28 The ERG stated that although an indirect comparison between ofatumumab plus chlorambucil and bendamustine was associated with uncertainty, it believed that the evidence was of good enough quality to inform an approximate cost-effectiveness estimate. Using data from COMPLEMENT 1 and 02CLLIII, the ERG performed an exploratory unadjusted direct comparison between ofatumumab plus chlorambucil and bendamustine, calculating a hazard ratio for progression-free survival of 0.61 in favour of bendamustine. The ERG highlighted that this did not allow for any differences in patient characteristics between the 2 trials.

Company's economic model

Structure

- 3.29 The company submitted a de novo economic model that compared ofatumumab plus chlorambucil with chlorambucil alone in patients with previously untreated lymphocytic leukaemia who were ineligible for fludarabine-based therapy. It did not compare

ofatumumab plus chlorambucil with the other comparators in the NICE scope (rituximab plus chlorambucil, and bendamustine alone or plus rituximab), or evaluate ofatumumab plus bendamustine as an intervention. The company used a semi-Markov model that incorporated time-dependent transition probabilities. It had a cycle length of 3 months (with half-cycle correction) and a lifetime time horizon of 25 years. A discount rate of 3.5% was applied to costs and health benefits and the analysis was conducted from an NHS and personal social services perspective.

- 3.30 In the starting state, 2 identical patient cohorts entered the model and had ofatumumab plus chlorambucil or chlorambucil alone. The same chlorambucil regimen was used in the model as that used in COMPLEMENT 1, which the company believed to be the regimen used most often in the UK. In the next model cycle, patients moved to a different health state depending on whether they had a complete or partial response, progressive disease, or stable disease. Patients in the chlorambucil arm whose disease responded and did not progress within 12 months could have retreatment, modelled through a separate health state. After disease progression, patients could have up to 3 further lines of active therapy, or best supportive care.

Population

- 3.31 The population in the company's model was the intention-to-treat population from COMPLEMENT 1, which had a median age of 67.7 years and a mean of 3.0 comorbidities. The company said that these patients represented 'less fit' patients who are expected to have less toxic therapy with chlorambucil rather than bendamustine. The company also noted that ofatumumab's marketing authorisation in the UK does not clearly define

‘ineligibility for fludarabine’ and concluded that the population in clinical practice could be broader than in its model.

Clinical parameters and variables

- 3.32 After beginning treatment in the starting state, patients were allocated to their best overall response state in the next model cycle. Patients were assigned to a response group (complete response, partial response or non-response) based on best response according to independent review during COMPLEMENT 1. The number of patients whose disease progressed after first-line treatment and those who died in each model cycle was determined using parametric survival functions. These were fitted to patient-level data from COMPLEMENT 1 for progression-free survival (assessed by an independent review committee) and for overall survival. Best response was included as a covariate for progression-free survival, enabling time to progression to be described for each response state. It was assumed in the base case that after trial follow-up there was no continuation of any treatment effect, and that the risk for death was equal in the 2 patient groups. The probability of transitioning to death did not depend on the health state.
- 3.33 For progression-free survival, the company chose to fit the log-normal distribution applied independently to the treatment arms based on statistical fit, diagnostic plots and visual inspection of the fit to the Kaplan–Meier data. The company observed that although several parametric functions provided a good visual fit to the Kaplan–Meier data for overall survival from COMPLEMENT 1, these were either clinically implausible or highly uncertain. Consequently, it used external long-term data (from study C9011) to guide the shape of the extrapolation after COMPLEMENT 1 using a Weibull distribution. C9011, which compared fludarabine

with chlorambucil in patients with untreated chronic lymphocytic leukaemia, had long-term data from 193 patients over a period of 18 years. In its economic model, the company applied an overall survival hazard ratio of 0.82 for ofatumumab plus chlorambucil compared with chlorambucil.

Retreatment and subsequent lines of treatment

3.34 The company advised that retreatment with chlorambucil is common practice in the NHS. In the base case, patients having chlorambucil alone whose disease responded and did not progress within 12 months could be retreated at disease progression (14.8% of patients, based on COMPLEMENT 1 data). The probability of response to retreatment was assumed to be the same as that at first-line treatment. Retreatment with ofatumumab plus chlorambucil was explored in a scenario analysis.

3.35 Following disease progression after first-line therapy, it was assumed that patients could have up to 3 further lines of treatment (based on clinical expert opinion). These later-line treatment options were:

- rituximab plus bendamustine
- fludarabine, cyclophosphamide and rituximab
- bendamustine
- rituximab plus chlorambucil
- chlorambucil alone.

The company explained that it is common for patients' physical fitness to improve after first-line therapy, making them eligible for fludarabine-based treatments (where before they may not have been). The proportion of each treatment given as second-, third- or fourth-line therapy in the model was based on market research

data and the pattern was assumed to be identical for both types of first-line treatment.

- 3.36 Following first-line treatment, the proportion of patients having active treatment after disease progression was estimated using pooled data for the 2 arms of COMPLEMENT 1. The proportion of patients whose disease responded to initial therapy and then had second-line treatment after progression was 47.1% in the chlorambucil alone group (an additional 14.8% had chlorambucil retreatment, giving a total of 61.9% of patients having active treatment after disease progression) and 61.9% in the ofatumumab plus chlorambucil group. For patients whose disease did not respond to initial therapy, it was assumed that 61.9% had second-, third- and fourth-line therapy treatment (irrespective of initial treatment). Health outcomes for later treatments were assumed to be equal, irrespective of first-line treatment. Because the available data for later-line treatment were limited, data from first-line trials were used for certain therapies.

Adverse events

- 3.37 The company's economic model included adverse events based on findings from the company's systematic review of clinical data. The company identified those adverse events which had with a risk difference of over 2% between the 2 comparators, or a risk of 5% or over for first-line therapies. It also considered the adverse events included in the model used in the appraisal for NICE's technology appraisal guidance on [bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#). After taking into account clinical expert advice, the company included the following adverse events in its economic model because they were expected to have an impact on cost or quality of life:

- anaemia (grades 3–4)
- diarrhoea (grades 1–2)
- febrile neutropenia (grades 3–4)
- infusion-related toxicity (grades 3–4)
- nausea/vomiting (grades 1–2)
- neutropenia (grades 3–4)
- pneumonia and other infections (grades 3–4)
- progressive multifocal leukoencephalopathy (grades 3–4; first-line treatment only)
- pyrexia (grades 3–4).

Although progressive multifocal leukoencephalopathy had not occurred in the ofatumumab clinical trials, the company included it in the economic model following clinical expert advice (assumed to develop in 1 in 1000 patients and have a 90% probability of death).

Transition probabilities

3.38 The transition probabilities for each health state were calculated using the area under the curve method with the progression-free and overall survival functions derived from COMPLEMENT 1 data. For first-line treatment, risks of disease progression and death were allowed to vary over time, consistent with the chosen survival functions. For later treatment lines, transition probabilities were derived from literature and a constant hazard was assumed.

Utility values

3.39 Patient-level data from COMPLEMENT 1 were used to derive a baseline utility value of 0.75, which was used during active first-line treatment and as the baseline utility value throughout the economic model. The changes in utility value from baseline for the different response groups were also derived from patient-level data from COMPLEMENT 1 (0.03 for complete response, 0.04 for partial

response and 0.01 for stable disease). A utility decrement of –0.10 was assumed for disease progression and subsequent treatment (retreatment; second-, third- and fourth-line treatment; best supportive care). This was derived from the literature (Beusterien et al. 2010); the company noted that this was consistent with the approach used in NICE’s technology appraisal guidance on [bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#).

- 3.40 Disutilities were applied for adverse events, with decrements ranging from –0.05 (for nausea/vomiting [grades 1–2]) to –0.20 (pneumonia and infections, progressive multifocal leukoencephalopathy and infusion-related toxicity [all grades 3–4]). It was assumed that adverse events decreased health-related quality of life for 0.5 weeks and utility loss was incurred only in the first 2 model cycles (except progressive multifocal leukoencephalopathy, which was assumed to last until death).

Costs

- 3.41 In the company’s economic model, the costs of first line-treatment comprised drug, administration and monitoring costs. Drug costs were taken from the British National Formulary 2014, with the average cost of £12,106 for 6 cycles at ofatumumab’s list price (£11,466 for 6300 mg of ofatumumab) and £640 for chlorambucil. The patient access scheme was applied to the cost of ofatumumab as a simple discount on the list price (the level of the discount is confidential). Costs were modelled separately for each response category (complete response, partial response, and no response). It was assumed that the duration of first-line treatment in COMPLEMENT 1 was representative of routine clinical practice (patients in COMPLEMENT 1 had a mean of 6.4 cycles of ofatumumab plus chlorambucil or 6.0 cycles of chlorambucil alone).

Monitoring costs during treatment were taken from NICE's technology appraisal guidance on [bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#). Administration costs were taken from NHS Reference Costs 2012/13. Costs for managing adverse events associated with first-line treatment were also largely taken from the [NICE technology appraisal guidance on bendamustine](#) and were assumed to be incurred only during the first 2 model cycles (except for those costs associated with progressive multifocal leukoencephalopathy).

3.42 Costs for drug retreatment were calculated as a weighted average, according to retreatment response rates, and added to the mean drug and administration costs for each response health state. The drug and administration costs for second-, third-, and fourth-line treatment were the same for all patients (that is, regardless of whether their first-line treatment was ofatumumab plus chlorambucil or chlorambucil alone). Weighted average drug and administration costs for each of the different regimens described in section 3.35 were calculated according to the percentage of patients having subsequent active treatment. Weighted average adverse event costs for each of the subsequent treatment regimens were calculated from the incidence of adverse events, with a further calculation made for each line of treatment.

3.43 Health-state costs comprised haematologist visits, routine testing and (for progressive disease or best supportive care) blood transfusions. It was assumed that all patients in the progressive disease state would have a blood transfusion every 3 weeks. The company advised that the frequencies informing the health-state costs were taken from the ERG report for NICE's technology appraisal guidance on [bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#). Health-state costs for each

3-month cycle were £440.89 for stable disease, £220.45 for partial response, £220.45 for complete response and £1100.92 for progressive disease or best supportive care.

Company's base-case results and sensitivity analyses

- 3.44 When using the price for ofatumumab that incorporated the patient access scheme (PAS), treatment with ofatumumab plus chlorambucil was associated with higher costs and greater quality-adjusted life year (QALY) gains than chlorambucil alone. The deterministic incremental cost-effectiveness ratio (ICER) incorporating the ofatumumab PAS was £23,414 per QALY gained (incremental costs and QALYs are commercial in confidence).
- 3.45 The company explored structural uncertainty in the model using univariate sensitivity analyses by individually varying key parameters by $\pm 10\%$. The ICERs for ofatumumab plus chlorambucil compared with chlorambucil alone that incorporated the PAS ranged from £18,796 to £28,032 per QALY gained. The ICER was most sensitive to changes in the proportion of patients having active treatment after progression (second- and third-line treatment) and to changes in the utility values at baseline and after first progression.
- 3.46 The company's probabilistic sensitivity analyses investigated the probability of ofatumumab plus chlorambucil being cost effective compared with chlorambucil alone. Using the PAS price gave a probability of cost effectiveness of 42% at a maximum acceptable ICER of £20,000 per QALY gained and 67% at a maximum acceptable ICER of £30,000 per QALY gained.
- 3.47 The company conducted scenario analyses that further explored structural uncertainty by changing the source of 1 parameter while maintaining the base case for other parameters. These included

changing the treatment effect by using investigator- assessed outcomes, exploring alternative parametric survival functions, and assuming no continued treatment benefit after follow-up. Other analyses included changing the proportion of patients who had later lines of active therapy, and choosing alternative sources for utility values. All of the scenario analyses that incorporated the PAS produced ICERs that were less than £30,000 per QALY gained.

ERG comments

- 3.48 The ERG considered the company's economic model to be generally appropriate. It found that the model was mostly completed to the standards of the NICE reference case and was largely well reported and conducted. However, the ERG identified an important error concerning the costs of third-line treatment. Moreover, it did not accept that all relevant comparators had been included.
- 3.49 The ERG was satisfied that the company's model structure for the period before disease progression was appropriate. However, taking into consideration the extreme uncertainty in the differences in total QALYs between the 2 treatment arms after progression, the poor quality of evidence of the utility values, and a large number of assumptions relating to costs, it considered the post-progression modelling to be overly complicated (see sections 3.51–3.53 below for details). The ERG therefore used an alternative method for the post-progression modelling in its own exploratory analyses (see section 3.55).
- 3.50 The ERG considered the population in the company's economic model to be sufficiently similar to patients in clinical practice, and that the company's long-term overall survival modelling guided by external data (Rai et al, 2009) was reasonable. It agreed with the

company that the patient population covered by ofatumumab's European marketing authorisation for untreated chronic lymphocytic leukaemia should be split into 2 subpopulations: those who are suitable for bendamustine treatment and those who are not. The ERG believed that rituximab plus chlorambucil, and bendamustine, should be included as comparators in the company's economic model in addition to chlorambucil. However, it considered it reasonable not to include bendamustine plus rituximab because the relevant trial data have not yet been published.

3.51 The ERG was aware that the company had modelled long tails for progression-free survival (that is, some people remained progression free for a long time). The ERG received clinical advice that although this might be appropriate for a younger population, it did not apply to patients who are ineligible for fludarabine. The ERG was also unable to find any evidence in the scientific literature that supported the company's approach. The ERG considered that a Weibull distribution, fitted independently to the ofatumumab plus chlorambucil and chlorambucil alone curves, was most the appropriate distribution based on statistical testing of the fit, visual inspection and a preference for a shorter tail. The ERG highlighted that there was extreme uncertainty in the difference between the 2 treatments in total QALYs after progression because the hazard ratio for overall survival is largely unknown for most of the time that patients are alive.

3.52 The ERG reviewed the utility values used in the company's economic model. It noted that the EQ-5D was used in COMPLEMENT 1 and considered this to be the best source of utility data for untreated chronic lymphocytic leukaemia. It calculated the weighted average utility value for the UK general

population at 68 years (the mean age of patients entering the model) to be 0.79, noting that the baseline utility of 0.75 was consistent with this. It noted that the true utility value at baseline was likely to be lower than that for the general public, given that the population in the model had chronic lymphocytic leukaemia and comorbidities. The ERG was surprised that the modelled utility values for complete response and partial response (0.78 and 0.79 respectively) were virtually identical to the utility value for the general population, but accepted them because they were taken from a high-quality data source. The ERG considered the quality of evidence for utility values after progression to be much poorer, and noted that there were insufficient data to adjust quality of life according to response to later lines of treatment. However, it accepted the company's value of 0.65 for progressive disease and noted that this was less than the age-adjusted utility value for the general public (estimated to be 0.77), as would be expected. The ERG noted that although the company said it had adopted a disutility of 0.10 for all states after progression to be consistent with NICE technology appraisal guidance on [bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#), the model in that appraisal had in fact assumed a utility value of 0.60 (instead of 0.65) for progressive disease. The ERG found that eliminating disutilities due to adverse events had only a minimal effect on the ICER.

- 3.53 The ERG largely agreed with the company's approach to modelling the costs for drug acquisition, drug administration and monitoring for the different lines of treatment. It was satisfied with the assumptions regarding supportive care in the model in all health states, except for the frequency of blood transfusions. Based on clinical expert advice, the ERG considered it more appropriate to assume that patients would have a blood transfusion every

4 weeks only in the last 6 months of life, rather than once every 3 weeks for the duration of their time in that health state.

3.54 The ERG considered the company's approach to modelling the costs of adverse events to be appropriate. It found the assumption that patients would have retreatment to be acceptable, but considered it more appropriate to assume the same proportion of retreatment with ofatumumab plus chlorambucil as with chlorambucil alone. It further noted that retreatment at the investigator's discretion in COMPLEMENT 1 may not be wholly relevant because it may not accurately reflect NHS practice. It also identified an error in the costs for third-line treatment and corrected this in its exploratory analyses (see section 3.55). However, although it found some assumptions in modelling costs to be plausible individually, the large number of assumptions combined to give substantial uncertainties in total costs, especially given the lack of evidence from the company for some assumptions affecting total costs. These included the assumption that patients' disease would not be retreated with ofatumumab plus chlorambucil, that the proportion of patients having later lines of treatment was equal for both arms, and that the proportion of patients having third- and fourth-line treatment was equal to that having second line.

ERG exploratory analyses

3.55 The ERG built an independent, simplified version of the company's model for its exploratory analyses because it believed that a simpler modelling structure was more appropriate after disease progression (owing to a lack of suitable data). Instead of using discrete model cycles, the ERG estimated QALYs and costs by applying unit costs and utilities to the undiscounted life-year estimates for each treatment in each arm in the company's model,

then applying discounting factors to the mean time in each particular health state.

3.56 The ERG included rituximab plus chlorambucil as a comparator. It used a progression-free survival distribution for rituximab plus chlorambucil that was equal to that for ofatumumab plus chlorambucil (this was assumed to follow a log-normal distribution in the ERG's exploratory analyses using the company's base-case assumptions, and a Weibull distribution in the ERG's exploratory base case). For overall survival, the ERG estimated the hazard ratio for rituximab plus chlorambucil compared with chlorambucil alone as 0.66 during the trial period, then set it to 1 after this time. In the ERG's exploratory base case, mean undiscounted survival after disease progression was assumed to be equal for all comparators, including rituximab plus chlorambucil. Costs (except for acquisition and administration costs), resource use, utility values and adverse events in the rituximab plus chlorambucil arm were all assumed to be equal to those for the ofatumumab plus chlorambucil arm.

3.57 The ERG's exploratory base case differed from the company's as follows:

- The ERG assumed that after disease progression, mean undiscounted QALYs and costs were equal between treatment arms. These were set to the values for the chlorambucil alone arm.
- The ERG assumed an equal number of blood transfusions in each arm (in the last 6 months of life only).
- Based on statistical analysis, visual inspection and a preference for a shorter tail, the ERG believed that a Weibull distribution, fitted independently to chlorambucil alone and to ofatumumab

plus chlorambucil, was the most appropriate option for extrapolating progression-free survival.

- The ERG corrected an error in modelling third-line treatment costs by assuming that all third-line costs were equal in the 2 treatment arms.

3.58 The ERG’s exploratory base-case results are presented in Table 1. For ofatumumab plus chlorambucil compared with chlorambucil alone, applying all 4 of the changes produced an ERG exploratory base-case ICER incorporating the PAS of £26,000 per QALY gained. The ERG noted that this was highly uncertain because of the uncertainty in costs and QALYs after disease progression. For ofatumumab plus chlorambucil compared with rituximab plus chlorambucil, using the patient characteristics from COMPLEMENT 1, the ERG estimated that the total costs and QALYs for the 2 treatment regimens were almost identical when using the PAS price for ofatumumab. The ERG noted that this was very highly uncertain because of issues associated with the indirect comparison of the 2 regimens (specifically, the different doses of chlorambucil in the 2 randomised controlled trials), as well as the uncertainty in costs and QALYs after progression.

Table 1 ERG exploratory base-case ICERs (incorporating the ofatumumab PAS)

		Ofatumumab + chlorambucil vs chlorambucil	Ofatumumab + chlorambucil vs rituximab + chlorambucil
	Company base-case assumptions	23,000	Total costs and QALYs very similar
1	Total undiscounted costs and QALYs in progressive disease equal in all arms	22,000	Total costs and QALYs very similar

2	Number of blood transfusions in progressive disease equal across treatments	28,000	Total costs and QALYs very similar
3	Progression-free survival Weibull, independent treatment arms (GSK log-normal)	26,000	Total costs and QALYs very similar
4	Costs of third-line drugs corrected	27,000	Total costs and QALYs very similar
2 + 3		30,000	Total costs and QALYs very similar
2 + 4		21,000	Total costs and QALYs very similar
2 + 3 + 4		33,000	Total costs and QALYs very similar
ERG's exploratory base-case ICER (1+2+3+4)		26,000	Total costs and QALYs very similar
Abbreviations: ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.			

3.59 The ERG conducted several exploratory sensitivity analyses of the comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil, using patient baseline characteristics either unadjusted from the relevant trials or adjusted to match those in CLL11. These caused ofatumumab plus chlorambucil (using the price incorporating the PAS) to be dominated by rituximab plus chlorambucil (that is, it was more expensive and less effective).

3.60 For completeness, the ERG estimated the approximate cost effectiveness of ofatumumab plus chlorambucil compared with bendamustine. It used an estimated progression-free survival hazard ratio for ofatumumab plus chlorambucil compared with bendamustine of 0.61 in favour of bendamustine. It concluded that it was highly likely that bendamustine alone dominates ofatumumab plus chlorambucil when using the PAS price for ofatumumab (that is, it costs less but is more effective).

3.61 Full details of all the evidence are in the [Committee papers](#).
[Editors to add unique identifier from website in-development page to complete hyperlink].

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ofatumumab, having considered evidence on the nature of chronic lymphocytic leukaemia and the value placed on the benefits of ofatumumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the treatment pathway for untreated chronic lymphocytic leukaemia. It heard from the clinical and patient experts that the key aims of treatment are to prolong progression-free survival and time to next treatment. It also heard from patient experts that this improves quality of life by increasing time away from hospitals and avoiding the psychological impact of relapse. It then heard from clinical experts that patients are treated with the most effective treatment that they can tolerate to achieve these aims, and that fludarabine, cyclophosphamide and rituximab would be offered to people with untreated chronic lymphocytic leukaemia, if they are fit enough to tolerate this combination. The Committee heard that for those patients who are not physically fit enough to tolerate fludarabine, cyclophosphamide and rituximab, treatment with a bendamustine-based regimen would be considered. However, the Committee heard that although bendamustine is considered to be less toxic than the combination of fludarabine, cyclophosphamide and rituximab, many patients are still too frail to tolerate bendamustine-based regimens. It heard that patients who are not fit enough to tolerate bendamustine but are fit enough for active treatment would have either rituximab plus chlorambucil or chlorambucil alone. The Committee therefore concluded that in patients who are ineligible for fludarabine-based treatment, the treatment pathway contained 2 distinct

subpopulations: those who are eligible to take bendamustine-based treatment and those who are not.

- 4.3 After discussing the current treatment pathway in the NHS in England, the Committee reviewed the relevance of the interventions specified in the NICE appraisal scope. It noted that the available clinical evidence for ofatumumab plus bendamustine consisted of 1 ongoing single-arm phase II trial (OMB115991), and that the company considered that these clinical trial results could not reliably inform relative clinical-effectiveness estimates compared with the comparators in the NICE appraisal scope. The Committee considered that the clinical trial results were associated with considerable uncertainty and concluded that the current results of OMB115991 could not be used to reliably inform its decision-making. For this reason, the Committee did not consider ofatumumab plus bendamustine any further and was therefore unable to make a recommendation on this treatment combination.
- 4.4 Having agreed that the fludarabine-ineligible population could be divided into patients who were eligible for bendamustine and those who were not, the Committee discussed the relevance of the bendamustine-containing comparators for ofatumumab and chlorambucil in the NICE appraisal scope. It noted the hierarchical nature of treatment based on fitness for treatment, and heard from the clinical experts that they would assess the suitability of a bendamustine-based regimen for fludarabine-ineligible patients before considering other types of treatment. The Committee therefore concluded that bendamustine-containing regimens were not relevant comparators for ofatumumab plus chlorambucil because they would be given to a different, fitter patient population in current clinical practice in England.

4.5 The Committee then discussed the relevance of the other comparators for ofatumumab plus chlorambucil in the NICE appraisal scope, specifically chlorambucil alone and chlorambucil plus rituximab (which is an anti-CD20 antibody, like ofatumumab). It noted that both the company and the ERG considered chlorambucil to be a widely used comparator for this patient population, and heard the clinical experts confirm this. The Committee noted the company's belief that use of rituximab plus chlorambucil has been relatively limited and explored possible reasons for this. It heard that NICE technology appraisal guidance on [rituximab for the first-line treatment of chronic lymphocytic leukaemia](#) does not recommend rituximab plus chlorambucil for chronic lymphocytic leukaemia, owing to a lack of clinical trial evidence for the combination at the time of the appraisal. It heard from the clinical experts that there is variation in the availability of rituximab for this patient population because funding by NHS England is consequently not routinely available, which is likely to be limiting its use. The Committee noted that, since the technology appraisal guidance was published, evidence on the clinical efficacy of rituximab plus chlorambucil compared with chlorambucil alone has been provided in 2 arms of the phase III CLL11 trial. The CLL11 results showed that progression-free survival was significantly longer with rituximab plus chlorambucil than with chlorambucil alone (16.3 months and 11.1 months respectively, $p < 0.001$). The Committee also heard from clinical experts that health care professionals were experienced in using rituximab (for example, in combination with fludarabine and cyclophosphamide in people for whom this is appropriate) and in managing adverse reactions, notably infusion-related reactions. The Committee concluded that both rituximab plus chlorambucil and chlorambucil alone were relevant comparators for ofatumumab plus chlorambucil in

fludarabine-ineligible patients for whom bendamustine-containing regimens are unsuitable.

- 4.6 The Committee discussed the clinical effectiveness of ofatumumab plus chlorambucil compared with chlorambucil alone. It noted the relatively small number of events (deaths) in both arms during the limited trial follow-up period and agreed this made it difficult to form any conclusion about any possible benefit in overall survival. However, it concluded that the company's evidence from COMPLEMENT 1 showed that ofatumumab plus chlorambucil was more clinically effective than chlorambucil alone, as evidenced by statistically significantly longer progression-free survival and higher overall response rates (see sections 3.7 and 3.9).
- 4.7 The Committee discussed the clinical effectiveness of ofatumumab plus chlorambucil compared with rituximab plus chlorambucil. It was aware of the company's concerns about the robustness of any indirect comparisons using data from COMPLEMENT 1 and CLL11 because of differences in patient characteristics and trial design, but also that the ERG considered these concerns insufficient to render any indirect comparison invalid. It noted that the ERG's exploratory adjusted indirect comparison of the 2 regimens gave a progression-free survival hazard ratio of 0.96 in marginal favour of rituximab plus chlorambucil when using the COMPLEMENT 1 patient characteristics (see sections 3.24 and 3.25). It agreed with the ERG's interpretation that the results using the COMPLEMENT 1 patient characteristics suggested that adding either of these anti-CD20 antibodies (rituximab or ofatumumab) to chlorambucil had a similar effect on increasing progression-free survival. However, the Committee considered that the results of the adjusted indirect treatment comparison using CLL11 patient characteristics suggested that the risk of progression was lower

with rituximab plus chlorambucil than with ofatumumab plus chlorambucil, as shown by a hazard ratio of 0.70. The Committee was aware that validity of the indirect comparison was reliant on the reported trial characteristics, and considered which trial's patient characteristics were preferable for its decision-making. It noted that the dosage per cycle, planned duration of treatment and mean cumulative dose were all greater for the chlorambucil arm in COMPLEMENT 1 than in CLL11 (see section 3.18), and considered that this could potentially influence the relative treatment effect of adding an anti-CD20 antibody. The Committee noted that both the ERG and the company considered the chlorambucil treatment regimen used in COMPLEMENT 1 to be representative of clinical practice in England. The Committee concluded that the ERG's adjusted indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil using COMPLEMENT 1 patient characteristics was acceptable and should be used in its decision-making but noted the uncertainty implied by the ERG's adjusted indirect treatment comparison using the CLL11 patient characteristics, which favoured rituximab plus chlorambucil.

- 4.8 The Committee considered the structure of the company's economic model. It was satisfied with the pre-progression structure, but considered the complex modelling of health states after disease progression was inappropriate because of the weak evidence base for the utility values (see section 3.52) and a high number of assumptions related to cost. It accepted the simplification of the company's model in the ERG's exploratory analyses where post-progression costs and undiscounted QALYs were equal regardless of initial treatment. The Committee concluded that, after modifying the post-progression structure according to the ERG's exploratory

analyses, the company's economic model was structurally acceptable.

4.9 The Committee considered the clinical inputs used in the company's economic model for the comparison between ofatumumab plus chlorambucil and chlorambucil alone in people for whom bendamustine was not appropriate (see section 4.4). It was largely satisfied with the company's approach, but was concerned that the log-normal distribution used by the company to extrapolate progression-free survival for ofatumumab plus chlorambucil compared with chlorambucil could overestimate the proportion of patients whose disease did not progress after trial follow-up ended. The Committee noted that the ERG had received clinical advice that the 'long tail' of the log-normal extrapolation was not consistent with the likely outcomes for patients who were not fit enough to tolerate fludarabine (such as those enrolled in COMPLEMENT 1). It noted that the ERG's exploratory base-case analysis used the Weibull distribution, which has a shorter tail (that is, fewer patients remained progression free in the long term). The Committee concluded that using the Weibull distribution, as in the ERG's exploratory analyses, was more appropriate than the log-normal distribution used by the company for estimating long-term progression-free survival in this patient population.

4.10 The Committee considered the clinical inputs used in the company's economic model for the comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil. It noted that the company had not provided any cost-effectiveness estimates for this comparison because it had considered an indirect treatment comparison using data from COMPLEMENT 1 and CLL11 to be inappropriate. As described in section 4.7, the Committee considered the ERG's exploratory indirect treatment

comparisons between ofatumumab plus chlorambucil and rituximab plus chlorambucil using the COMPLEMENT 1 patient characteristics to be appropriate. The Committee found it reasonable that the ERG used a hazard ratio of 1 for progression-free survival in its exploratory base case (that is, it was assumed that the risk of progression was the same with both regimens). The Committee also believed it acceptable to assume equal response rates and overall survival because data limitations meant that it was not possible for the ERG to adjust the patient characteristics for these variables. It did, however, recall that the ERG's adjusted indirect treatment comparison using the CLL11 patient characteristics tended to favour rituximab plus chlorambucil. The Committee concluded that, although they were associated with uncertainty, the clinical inputs in the ERG's exploratory base case for the comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil, based on the indirect treatment comparison using COMPLEMENT 1 patient characteristics, were acceptable for its decision-making.

- 4.11 The Committee discussed the pre-progression utility values in the company's economic model. It appreciated that, in line with NICE's [Guide to the methods of technology appraisal 2013](#), the company had used EQ-5D data from the COMPLEMENT 1 trial to generate utility values for the pre-progression health states. The Committee considered the baseline utility value (0.75) to be higher than it would have expected because it was close to the value for the general population. However, it heard from the clinical experts that the high baseline value could be a result of patients in clinical trials sometimes being treated earlier than they would be in routine clinical practice (that is, before symptoms are reported). Conversely, it considered the improvement from baseline after a response or stable disease (0.01–0.04) to be lower than expected.

The Committee heard that this may be because the symptom improvement in the clinical trial was less than that seen in clinical practice because of high baseline utility, and because the EQ-5D was not sensitive enough to pick up improvement in disease symptoms or less worry and anxiety after remission. The Committee concluded that it accepted the utility values derived from COMPLEMENT-1 data because the EQ-5D is a standardised and validated generic instrument that is widely used and has been validated in many patient populations, as well as being NICE's preferred instrument.

- 4.12 The Committee considered the post-progression utility value in the company's economic model (0.65, taken from Beusterien et al. 2010). It was aware that although the company said it had adopted a disutility of 0.10 for all states after progression to be consistent with NICE technology appraisal guidance on [bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#), the ERG had noted that the model in that appraisal in fact assumed a utility value of 0.60 for progressive disease. The Committee noted that in the paper by Beusterien et al., 0.65 was the utility value associated with third-line treatment and that a utility value of 0.71 had been derived for second-line treatment. The Committee noted that the company's scenario analyses included other sources of post-progression utility values, including some derived from COMPLEMENT 1, and that the results were generally similar to or lower than the company's base-case ICER incorporating the PAS for ofatumumab plus chlorambucil compared with chlorambucil alone. Moreover, it was aware that accepting the ERG's assumption of equal costs and QALYs after disease progression reduced the effect of uncertainty around the post-progression utility value. The Committee concluded that although there was some uncertainty over what would be the most appropriate post-

progression utility value, this was not a key driver of the ICER and that 0.65 as used by the company in its base case was acceptable.

4.13 The Committee considered the costs used in the company's model. It broadly agreed with the acquisition, administration and health state costs used by the company, but accepted the ERG's correction of an error in third-line treatment costs and the reduction in blood transfusions so that patients had an equal number of transfusions every 4 weeks in the last 6 months of life, irrespective of initial treatment. The Committee concluded that costs in the ERG's exploratory base-case analyses using the company's model were the most appropriate for decision-making.

4.14 After considering the limited clinical evidence (see section 4.3) and absence of cost-effectiveness estimates, the Committee concluded it was unable to make a recommendation on the combination of ofatumumab plus bendamustine. The Committee then considered the most plausible cost-effectiveness estimate for ofatumumab plus chlorambucil compared with both chlorambucil alone and with rituximab plus chlorambucil:

- For the comparison with chlorambucil alone, the Committee accepted the assumptions in the ERG's base-case exploratory analyses that incorporated the ofatumumab PAS (with the 4 modifications to the company's base case, as described in sections 4.8, 4.9 and 4.13). This resulted in an ICER of £26,000 per QALY gained for ofatumumab plus chlorambucil compared with chlorambucil alone. It considered that the company's and ERG's sensitivity analyses showed that the ICER was sufficiently robust.
- The Committee noted that the ERG's base-case exploratory analyses that included the ofatumumab PAS did not include a numerically precise ICER for ofatumumab plus chlorambucil

compared with rituximab plus chlorambucil because the total costs and total QALYs were very similar. The Committee understood that these low incremental costs and health benefits meant that ICERs could vary dramatically in response to even small changes because of a pronounced effect on the cost-effectiveness ratio. It noted that the ERG's exploratory sensitivity analyses including the ofatumumab PAS, which used CLL11 patient characteristics to inform the adjusted indirect treatment comparison, showed that ofatumumab plus chlorambucil was dominated by rituximab plus chlorambucil (that is, it was more expensive and less effective). Overall, the Committee concluded that, when using the ofatumumab PAS price, the cost effectiveness of ofatumumab plus chlorambucil is likely to be similar to rituximab plus chlorambucil because of small differences in costs and QALYs. It noted that, when choosing either of these anti-CD20 antibodies (ofatumumab or rituximab) in combination with chlorambucil, clinicians may wish to consider which one has the lower acquisition cost, as well as their clinical experience in using that particular treatment (see section 4.5).

The Committee therefore recommended ofatumumab plus chlorambucil as a cost-effective use of NHS resources for untreated chronic lymphocytic leukaemia in people who are ineligible for fludarabine-based therapy, only if bendamustine is not suitable and the company provides ofatumumab with the discount agreed in the PAS.

- 4.15 The Committee deliberated about whether ofatumumab could be considered an innovative treatment. It noted that the company's evidence submission stated that all relevant health-related benefits were likely to be included in the QALY calculation and that the evidence submission did not describe any potential to make a

significant and substantial impact on health-related benefits. The Committee concluded that ofatumumab could not be considered an innovative treatment.

- 4.16 The Committee considered the potential equality issue raised by consultees that ofatumumab plus chlorambucil would especially benefit older people with comorbidities, who may be judged as unfit for treatment with other regimens. The Committee concluded that fitness for treatment drives treatment decisions, not age, and therefore there was no need to change its recommendations because of this issue.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title: Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia	Section
Key conclusion		
<p>The Committee recommended ofatumumab plus chlorambucil as a cost-effective use of NHS resources for untreated chronic lymphocytic leukaemia in people who are ineligible for fludarabine-based therapy, only if bendamustine is not suitable and the company provides ofatumumab with the discount agreed in the PAS.</p> <p>The Committee concluded that ofatumumab plus chlorambucil was more clinically effective than chlorambucil alone, as evidenced by statistically significantly longer progression-free survival and higher overall response rates, but was unable to form a conclusion about any possible benefit in overall survival.</p> <p>The Committee found it reasonable that, because of data limitations, the ERG assumed equal progression-free survival, response rates</p>		<p>4.6, 4.10, 4.14</p>

<p>and overall survival in its adjusted indirect comparison of ofatumumab plus chlorambucil and rituximab plus chlorambucil, as used in the ERG’s exploratory base case.</p> <p>After considering the limited clinical evidence and absence of cost effectiveness estimates for ofatumumab plus bendamustine, the Committee concluded it was unable to make a recommendation on this treatment combination.</p> <p>The Committee concluded the most plausible cost effectiveness estimate for ofatumumab plus chlorambucil compared with chlorambucil alone using the ofatumumab PAS price was the ERG’s base-case ICER of £26,000 per QALY gained for ofatumumab plus chlorambucil compared with chlorambucil alone, and that this ICER was sufficiently robust. The Committee concluded that the cost effectiveness of ofatumumab plus chlorambucil using the ofatumumab PAS price compared with rituximab plus chlorambucil is likely to be similar because of small differences in costs and QALYs.</p>		
Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard that the key aims of treatment are to prolong progression-free survival and time to next treatment, and that patients are treated with the most aggressive treatment that they can tolerate to achieve these aims</p>	<p>4.2</p>
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Ofatumumab (Arzerra, GlaxoSmithKline) is a fully human, monoclonal antibody that is targeted against the CD20 cell surface antigen of B-lymphocytes and causes cell death.</p> <p>The Committee noted that the company's evidence submission did not describe any potential to make a significant and substantial impact on health-related benefits, and concluded that ofatumumab could not be considered an innovative treatment.</p>	<p>2.1, 4.15</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee concluded that in patients who are ineligible for fludarabine-based treatment, the treatment pathway contained 2 distinct subpopulations: those who are eligible to take bendamustine-based treatment and those who are not. The Committee concluded that bendamustine-containing regimens were not relevant comparators for ofatumumab plus chlorambucil because they would be given to a different, fitter patient population. However, Committee concluded that both rituximab plus chlorambucil and chlorambucil alone were relevant comparators for ofatumumab plus chlorambucil in fludarabine-ineligible patients for whom bendamustine-containing regimens are unsuitable.</p>	<p>4.2, 4.5</p>

Adverse reactions	The summary of product characteristics lists the following adverse reactions for ofatumumab, alone or with an alkylating agent, as affecting more than 10% of patients: upper and lower respiratory tract infections, neutropenia, anaemia, nausea, rash and pyrexia.	2.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the available clinical evidence for ofatumumab plus bendamustine consisted of 1 ongoing single-arm phase II trial and concluded that its results were associated with considerable uncertainty. It did not consider ofatumumab plus bendamustine any further in the appraisal and was unable to make a recommendation on this treatment combination.	4.3
Relevance to general clinical practice in the NHS	The Committee noted that both the ERG and the company considered the chlorambucil treatment regimen used in COMPLEMENT 1 to be representative of clinical practice in England. The Committee concluded that the ERG's adjusted indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil using COMPLEMENT 1 patient characteristics was acceptable and should be used in its decision-making.	4.7

<p>Uncertainties generated by the evidence</p>	<p>The Committee noted the high overall survival rate in both arms of COMPLEMENT 1 during the trial follow-up period and agreed this made it difficult to form any conclusion about any possible survival benefit with ofatumumab.</p> <p>The Committee accepted the ERG's adjusted indirect comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil using COMPLEMENT 1 patient characteristics for its decision-making. It also noted the uncertainty implied by the ERG's adjusted indirect treatment comparison using the CLL11 patient characteristics, which favoured rituximab plus chlorambucil.</p>	<p>4.6, 4.7</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>Not applicable.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that COMPLEMENT 1 showed that ofatumumab plus chlorambucil was more clinically effective than chlorambucil alone, as evidenced by statistically significantly longer progression-free survival and higher overall response rates.</p>	<p>4.6</p>
<p>Evidence for cost effectiveness</p>		

<p>Availability and nature of evidence</p>	<p>The Committee concluded that, after modifying the post-progression structure according to the ERG’s exploratory analyses, the company’s economic model was structurally acceptable.</p>	<p>4.8</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee was concerned that the log-normal distribution used by the company to extrapolate progression-free survival for ofatumumab plus chlorambucil compared with chlorambucil could overestimate the proportion of patients whose disease did not progress after trial follow-up ended. It concluded that using the Weibull distribution, as in the ERG’s exploratory analyses, was more appropriate than the log-normal distribution used by the company for estimating long-term progression-free survival in this patient population.</p> <p>The Committee accepted the clinical inputs in the ERG’s exploratory base case for the comparison between ofatumumab plus chlorambucil and rituximab plus chlorambucil, based on the indirect treatment comparison using COMPLEMENT 1 patient characteristics. It did, however, recall that the ERG’s adjusted indirect treatment comparison using the CLL11 patient characteristics tended to favour rituximab plus chlorambucil.</p>	<p>4.9, 4.10</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee concluded that it accepted the pre-progression utility values derived from COMPLEMENT 1 data because the EQ-5D is a standardised and validated generic instrument that is widely used and has been validated in many patient populations, as well as being NICE's preferred instrument.</p> <p>The Committee noted that although there was uncertainty around the most appropriate post-progression utility value, it concluded that was not a key driver of the ICER and that value used by the company in its base case was acceptable.</p> <p>The Committee noted that the company's evidence submission stated that all relevant health-related benefits were likely to be included in the QALY calculation.</p>	<p>4.11, 4.12, 4.15</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Not applicable.</p>	

<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee noted that the ERG’s base-case exploratory analyses for ofatumumab plus chlorambucil compared with rituximab plus chlorambucil used an adjusted indirect comparison derived from COMPLEMENT 1 patient characteristics. This gave very similar total costs and total QALYs when the ofatumumab PAS was incorporated. It recalled that the ERG’s exploratory sensitivity analyses, which used CLL11 patient characteristics to inform the adjusted indirect treatment comparison, showed that ofatumumab plus chlorambucil was dominated by rituximab plus chlorambucil when the ofatumumab PAS price was used (that is, it was more expensive and less effective).</p>	<p>4.10, 4.14</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee concluded that the ERG’s exploratory base-case ICER of £26,000 per QALY gained, which incorporated the ofatumumab PAS, was the most plausible for ofatumumab plus chlorambucil compared with chlorambucil alone.</p> <p>The Committee concluded that, when using the ofatumumab PAS price, the cost effectiveness of ofatumumab plus chlorambucil is likely to be similar to rituximab plus chlorambucil because of small differences in costs and QALYs.</p>	<p>4.14</p>
<p>Additional factors taken into account</p>		

Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health that makes ofatumumab available with a discount. The size of the discount is commercial in confidence.	2.3
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	The Committee concluded that there was no need to change its preliminary recommendations because of any potential equality issues.	4.16

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that ofatumumab is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.3 The Department of Health and the manufacturer have agreed that ofatumumab will be available to the NHS with a patient access scheme which makes ofatumumab available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the [NICE Patient Access Liaison Unit \(PASLU\)](#) .

5.4 NICE has developed tools to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

- [Bendamustine for the first-line treatment of chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 216 (2011).

- [Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab](#). NICE technology appraisal guidance 202 (2010).
- [Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 193 (2010).
- [Rituximab for the first-line treatment of chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 174 (2009).
- [Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 119 (2007).
- [Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia](#). NICE technology appraisal guidance 29 (2001).
- [Improving outcomes in haematological cancers](#). NICE cancer service guidance (2003).

Under development

- Obinutuzumab for previously untreated chronic lymphocytic leukaemia' NICE technology appraisal guidance, publication expected February 2015.

7 Proposed date for review of guidance

- 7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
October 2014

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel

Institute of Brain and Behaviour Mental Health, University of Manchester

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

Mr David Chandler

Lay member

Mrs Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Dept of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Ms Emily Lam

Lay member

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Suzanne Martin

Reader in Health Sciences

Dr Iain Miller

Founder & CEO, Health Strategies Group

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School / Senior Clinical University
Teacher, University of Glasgow

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS
Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of
Sheffield

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related
Research, University of Sheffield

Dr Judith Wardle

Lay member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more
health technology analysts (who act as technical leads for the appraisal), a
technical adviser and a project manager.

Linda Landells

Technical Lead

Eleanor Donegan

Technical Adviser

Nicole Fisher

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group:

- Hoyle, M, et al. Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia: a critique of the submission from GSK, September, 2014.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- GlaxoSmithKline

II. Professional/specialist and patient/carer groups:

- Chronic Lymphocytic Leukaemia Support Association
- Leukaemia CARE
- Lymphoma Association
- British Society for Haematology
- Cancer Research UK
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Napp Pharmaceuticals
- Roche Products
- Peninsula Technology Assessment Group
- National Institute for Health Research
- Health Technology Assessment Programme
- National Collaborating Centre for Cancer
- National Institute for Health and Care Excellence

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on ofatumumab by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Scott Marshall, nominated by The Royal College of General Practitioners– clinical specialist
- Dr Francesco Forconi, nominated by The Royal College of General Practitioners– clinical specialist
- Nick York, nominated by the Chronic Lymphocytic Leukaemia Support Association– patient expert

- Jackie Martin, nominated by the Chronic Lymphocytic Leukaemia Support Association– patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline