Ofatumumab, a fully human anti-CD20 monoclonal antibody, in biological-naive, rheumatoid arthritis patients with an inadequate response to methotrexate: a randomised, double-blind, placebo-controlled clinical trial

Peter C Taylor,1 Emilia Quattrocchi,2 Stephen Mallett,2 Regina Kurrasch,3 Jørgen Petersen,4 David J Chang3

ABSTRACT

Objectives To evaluate the efficacy and safety of intravenous ofatumumab, a fully human anti-CD20 monoclonal antibody, in biological-naive, active rheumatoid arthritis (RA) patients despite methotrexate treatment.

Methods In this double-blind, placebo-controlled, phase III study, active RA patients on stable methotrexate were randomly assigned to one course of two infusions of ofatumumab 700 mg (n = 130) or placebo (n = 130), 2 weeks apart. The primary endpoint was the ACR20 response at week 24. Secondary endpoints included ACR50/70, EULAR response, disease activity score based on 28 joints using C-reactive protein, adverse events (AE) and immunogenicity.

Results At week 24, a greater proportion of patients on ofatumumab compared with placebo achieved an ACR20 response (50% vs 27%, p<0.001) and a good or moderate EULAR response (67% vs 41%, p<0.001). All other key secondary efficacy endpoints were significantly improved on ofatumumab. Efficacy observed by 8 weeks was sustained throughout the study. The most common AE for ofatumumab versus placebo were rash (21% vs <1%) and urticaria (12% vs <1%), mostly occurring on the first infusion day. Overall, first-dose infusion reactions were 68% for ofatumumab and 6% for placebo, mostly mild to moderate; second-dose infusion reactions markedly declined (<1% and 0%). Serious AE were reported in 5% of ofatumumab versus 3% of placebo patients. Infection rates were 32% and 26% (serious infections <1% and 2%), respectively. One death (interstitial lung disease), unrelated to study drug, was reported on ofatumumab. No antidrug antibodies were detected in ofatumumab patients.

Conclusions Ofatumumab significantly improved all clinical outcomes in biological-naive, active RA patients with no detectable immunogenicity at week 24. No unexpected safety findings were identified.

Trial Registry clinicaltrials.gov registration number NCT00611455

Ofatumumab (HuMax-CD20) is a human IgG1κ lytic monoclonal antibody (mAb) that specifically binds to the human CD20 antigen inducing potent B-cell lysis. The CD20 antigen is expressed only by B lymphocytes from the pre-B to the plasma-cytoid immunoblast stage. Ofatumumab recognises a unique membrane-proximal epitope on the human CD20 molecule, distinct from the epitope recognised by rituximab1 or by other anti-CD20 mAb.2,3 The membrane proximity of this epitope probably accounts for the high efficiency of B-cell killing observed with ofatumumab in both in-vitro and in-vivo preclinical studies.4–7

In animal models, ofatumumab induced selective and prolonged B-cell depletion primarily mediated by effective complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.5–9 Effective complement-dependent cytotoxicity may depend on the distance between the plasma membrane and the constant parts of the sensitising antibody thus enabling the efficient and rapid engagement of complement activation.10

A phase I/II study of ofatumumab, administered as two intravenous infusions of 300, 700 or 1000 mg 2 weeks apart, in active rheumatoid arthritis (RA) patients with an inadequate response to disease-modifying antirheumatic drugs (DMARD), demonstrated significant clinical benefit and reasonable tolerability (improved after the implementation of premedication) at all doses investigated when compared with placebo, with the 700 mg dose considered to be optimal.11

To characterise further the efficacy and safety profile of ofatumumab we conducted a placebo-controlled phase III trial in patients with active RA who had an inadequate response to methotrexate therapy and no previous biological treatment exposure. This trial was also designed to investigate the effects of ofatumumab on the extent and duration of B-cell depletion, biomarkers of clinical response, patient-reported outcomes and immunogenicity.

METHODS

Study design and objectives

This was a multicentre, randomised, double-blind, placebo-controlled, parallel group, phase III trial. Patients were enrolled at 36 sites in western Europe, eastern Europe, South America and Asia Pacific. The trial is registered at clinicaltrials.gov number NCT00611455. The first patient was enrolled in January 2008 and the last visit for the double-blind phase was in June 2009. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. All participating sites received approval from national, regional, or investigational centre ethics committee

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The trial included a 24-week double-blind, placebo-controlled period followed by a 120-week open-label extension and a safety follow-up. This paper summarises results from the completed, placebo-controlled, 24-week double-blind phase only.

Eligible patients were randomly assigned (1:1) to receive two infusions of either ofatumumab 700 mg or placebo 2 weeks apart (one course), added to their stable background methotrexate dose. Randomisation was stratified by rheumatoid factor (RF) seropositivity/negativity and region. GlaxoSmithKline prepared a computer-generated randomisation schedule and randomisation was handled centrally through an interactive voice response system. An unblinded pharmacist at each site prepared the infusions; ofatumumab and saline (placebo) infusions were indistinguishable. Other study personnel and patients were blinded to treatment allocation until the double-blind period was complete. Premedication with antihistamine (certirizine 10 mg or equivalent), oral paracetamol 1000 mg and intravenous methylprednisolone 100 mg was administered 30 min to 2 h before each infusion. Patients who did not respond were allowed non-biological DMARD rescue treatment from week 16; however, the use of rescue treatment precluded subsequent entry into the open-label period. Breakthrough pain management such as analgesics, non-steroidal anti-inflammatory drugs and one intra-articular corticosteroid injection in one joint per 6-month period were allowed. The joint receiving an intra-articular injection was scored as both swollen and tender in joint count assessments during the following 12-week period.

The primary objective was to evaluate the efficacy of ofatumumab compared with placebo based on the proportion of patients achieving an American College of Rheumatology (ACR) 2012 response at week 24. Secondary endpoints included proportions of patients achieving ACR50, ACR70, European League Against Rheumatism (EULAR) good or moderate responses, and mean changes in the disease activity score based on 28 joints (DAS28) using C-reactive protein (CRP), health assessment questionnaire disability index (HAQ–DI), short-form health survey (SF-36v2) and functional assessment of chronic illness therapy–fatigue version 4 (FACIT–F) at week 24.

**Patient population**

Male and non-pregnant, non-lactating female patients 18 years and older, diagnosed with active RA according to ACR 1987 criteria of RA functional class I, II or III of 6 months or more duration were eligible to participate. Active RA was defined as eight or more swollen and eight or more tender joint counts, based on 66/68 joint count; either CRP of 1.0 mg/dl or greater or erythrocyte sedimentation rate (ESR) of 22 mm/h or greater; and DAS28 based on ESR of 3.2 or greater. Patients were required to have an inadequate response to methotrexate and to be receiving methotrexate 7.5–25 mg/week for at least 12 weeks, and at a stable dose for at least 4 weeks, before baseline. All patients underwent a washout period of at least 4 weeks for all DMARDs (pentoxyfylline ≥12 weeks or administration of cholestyramine underwnted a washout period of at least 4 weeks for all DMARD) with stable methotrexate therapy, oral or institutional review boards; each patient provided written informed consent.

Clinical assessments of disease activity were performed at baseline and every 4 weeks to week 24 and included an evaluation of the 68-joint tender joint count and 66-joint swollen joint count conducted by an independent assessor (blinded to patient-rated outcomes), patient’s pain assessment (visual analogue scale (VAS) 0–100 mm), patient’s and physician’s global assessment of disease activity (VAS 0–100 mm), HAQ–DI and levels of acute-phase reactants (ESR and CRP). From these data, ACR20, ACR50 and ACR70 response rates, mean change in DAS28–ESR and DAS28–CRP and EULAR response were determined. FACIT–F and SF-36v2 were assessed at baseline, week 16 and week 24.

Laboratory investigations included levels of peripheral blood lymphocytes measured by fluorescence-activated cell sorting analysis by the surrogate marker CD19, peripheral T lymphocytes measured by CD3, CD4 and CD8 markers, immunoglobulins (IgA, IgM, IgG), RF and immunoglobulins to RF (IgM–RF, IgG–RF and IgA–RF), anticyclic citrullinated peptide antibodies (anti-CCP), acute phase serum amyloid A, interleukin 6 (IL-6) and C reactive protein (CRP) (all performed by Quest Diagnostics) and antibodies to ofatumumab measured using a validated electrochemiluminescence assay. Mesol-scale discovery immunoassay. Positive samples from the binding antibody assay were tested in a neutralisation antibody assay (Clinical Immunology, Biopharm R&D, GlaxoSmithKline, King of Prussia, PA, USA).

Adverse events (AE) and serious adverse events (SAE) were collected throughout the study and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 12. Infusion-related events occurring during study drug infusion and up to 24 h after completion of the infusion (and likely to represent clinical signs and symptoms characteristic of ofatumumab infusion reactions in patients with RA) were identified by a safety review team before unblinding. Low CD19 cell counts were not reported as AE and hospitalisation for completion of an infusion was not reported as a SAE. Infections were determined using the MedDRA system organ class ‘infections and infestations’.

**Sample size estimation**

A sample size of 124 subjects per group was estimated to provide at least 90% power to detect differences in the proportions of patients achieving an ACR20 response at week 24 between ofatumumab versus placebo, at a 5% level of significance. This was based on a $\chi^2$ test comparing two binomial proportions.

**Statistical analysis**

For categorical endpoints, the efficacy of ofatumumab versus placebo was analysed using the Cochran Mantel Haenszel test, adjusting for baseline stratification factors, RF status and geographical region (ie, eastern Europe, western Europe, South America, Asia Pacific). For continuous endpoints efficacy was analysed using analysis of covariance, adjusting for RF status, geographical region and baseline value. For categorical endpoints, patients who took disallowed medication or withdrew...
from the study were imputed as non-responders. For continuous endpoints, data were imputed by carrying forward the last value recorded before taking disallowed medication or withdrawal (last observation carried forward). The intent-to-treat (ITT) population comprised all randomly assigned patients who received at least one infusion of the study drug. The safety population was identical to the ITT population except that patients were analysed according to their actual treatment in case this differed from their randomised treatment.

RESULTS
Disposition of patients and baseline characteristics
A total of 344 patients was screened and 265 were enrolled and randomly assigned; the reasons for screening failure are shown in Figure 1. Of the 265 randomly assigned patients, 260 (98%) were exposed to investigational product and was included in the safety and ITT populations (Figure 1). One patient was randomly assigned to placebo but received ofatumumab and was included in the placebo group for the ITT population (based on randomised treatment) and in the ofatumumab group for the safety population (based on actual treatment received).

Demographics and baseline RA characteristics were balanced between the two groups (Table 1). Most patients were women (82%) and RF positive (84%), with a mean age of 53 years. At baseline, mean RA duration was 8.5 years, mean DAS28–CRP was 5.7 and mean DAS28–ESR was 6.5 (Table 1).

Clinical response
At week 24, a greater proportion of patients administered ofatumumab 700 mg achieved the primary endpoint of ACR20 compared with placebo (50% and 27%, respectively, p<0.001). In addition, significantly greater improvements in ACR50 and ACR70 were observed with ofatumumab versus placebo (ACR50 27% and 11%, p<0.001; ACR70 13% and 2%, p=0.001) (Table 2 and Figure 2). When examined by RF status, the ACR20 response in ofatumumab and placebo groups, respectively, was 50% (54/108) versus 26% (29/111) for seropositive patients and 46% (10/21) versus 30% (6/20) for seronegative patients. When examined by anti-CCP status,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics and baseline disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Ofatumumab 700 mg (n=129)</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>51.7 (11.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>106 (82.2)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>122 (94.6)</td>
</tr>
<tr>
<td>Mean (SD) disease duration, years</td>
<td>7.93 (7.2)</td>
</tr>
<tr>
<td>Median (min, max) methotrexate dose, mg/week</td>
<td>15.0 (7.5, 25)</td>
</tr>
<tr>
<td>Previous DMARD, n (%)</td>
<td>1–2</td>
</tr>
<tr>
<td>&gt;4</td>
<td>36 (27.9)</td>
</tr>
<tr>
<td>Patients receiving oral corticosteroid, n (%)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Median (min, max) oral corticosteroid dose, mg/day*</td>
<td>75 (58.1)</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>108 (83.7)</td>
</tr>
<tr>
<td>Median (min, max) CRP, mg/l</td>
<td>8.3 (0.98)</td>
</tr>
<tr>
<td>Mean (SD) ESR, mm/h</td>
<td>47.1 (25.3)</td>
</tr>
<tr>
<td>Mean (SD) total RF, IU/ml†</td>
<td>326.5 (593.6)</td>
</tr>
<tr>
<td>Mean (SD) SJC (66 joints)</td>
<td>16.2 (7.4)</td>
</tr>
<tr>
<td>Mean (SD) TJC (68 joints)</td>
<td>28.7 (13.3)</td>
</tr>
<tr>
<td>Mean (SD) DAS28–CRP</td>
<td>5.83 (0.79)</td>
</tr>
<tr>
<td>Mean (SD) DAS28–ESR</td>
<td>6.59 (0.82)</td>
</tr>
<tr>
<td>Mean (SD) HAQ–DI</td>
<td>1.7 (0.67)</td>
</tr>
<tr>
<td>Mean (SD) FACIT–F</td>
<td>25.2 (10.0)</td>
</tr>
</tbody>
</table>

* Prednisolone equivalent dose.
† At screening.
CRP, C-reactive protein; DAS28, disease activity score based on 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FACIT–F, functional assessment of chronic illness therapy–fatigue; HAQ–DI, health assessment questionnaire disability index; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.
Table 2  Summary of disease-activity and quality-of-life clinical endpoints at week 24 for patients receiving ofatumumab or placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ofatumumab 700 mg (n=129)</th>
<th>Placebo (n=131)</th>
<th>Adjusted mean difference (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>64/129 (50%)</td>
<td>35/131 (27%)</td>
<td>2.86 (1.67 to 4.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR50</td>
<td>35/129 (27%)</td>
<td>14/131 (11%)</td>
<td>3.29 (1.63 to 6.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR70</td>
<td>17/129 (13%)</td>
<td>3/131 (2%)</td>
<td>6.63 (1.87 to 23.51)</td>
<td>0.001</td>
</tr>
<tr>
<td>EULAR response*</td>
<td>87/129 (67%)</td>
<td>54/131 (41%)</td>
<td>3.07 (1.82 to 5.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical remission†</td>
<td>13/129 (10%)</td>
<td>7/131 (5%)</td>
<td>2.09 (0.76 to 5.77)</td>
<td>0.152</td>
</tr>
<tr>
<td>HAG–DI response‡</td>
<td>74/129 (57%)</td>
<td>59/131 (45%)</td>
<td>1.65 (1.01 to 2.70)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

**Results are reported in accordance with EULAR/ACR collaborative recommendations.**

**ACR20/50/70, 20%/50%/70% improvement as per American College of Rheumatology (ACR) criteria.**

*EULAR response of moderate or good, based on DAS28–CRP.

†DAS28–CRP score less than 2.6.

‡Change from baseline HAG–DI score of 0.22 or greater.

*Negative change represents an improvement. Patient numbers assessed: placebo (n=130); ofatumumab (n=126).

**Patient numbers assessed: placebo (n=117); ofatumumab (n=110).

The ACR20 response in ofatumumab and placebo groups, respectively, was 50% (56/111) versus 26% (29/113) for seropositive patients and 44% (7/16) versus 31% (5/16) for seronegative patients.

All other secondary efficacy endpoints, including EULAR response and mean change from baseline in DAS28–CRP and DAS28–ESR were significantly improved in the ofatumumab group compared with placebo, except for clinical remission (DAS28–CRP <2.6) (table 2 and supplementary table S1, available online only). The mean change from baseline in DAS28–CRP scores over the 24-week period showed sustained improvement compared with placebo from week 8 to week 24 (figure 3). Ofatumumab also provided improvements in patient-reported outcomes as shown by significantly greater changes from baseline in HAQ–DI, FACIT–F and SF36v2 scores compared with placebo (table 2).

Laboratory findings

Peripheral B lymphocytes (CD19) were greatly reduced at each visit relative to baseline in the ofatumumab group: median reductions at weeks 2 (before the second infusion), 4, 12 and 24 were 95%, 96%, 96% and 94%, respectively. In the placebo group, CD19 cells increased by 3% at week 24. In the ofatumumab group one patient (1%) had a CD19 B-cell count equal to or greater than the lower limit of normal (0.11 GI/l) or the baseline value at week 24. No trend for a change in peripheral CD3, CD4 or CD8 T-cell counts was observed in either CD3, CD4 or CD8 T-cell counts was observed in either group.

Biomarkers and assessment of immunogenicity

At week 24, the median change from baseline in absolute biomarker levels for ofatumumab and placebo, respectively, were: −4.0 versus −0.4 ng/l for IL-6; −5.5 versus −10.9 mg/ml for serum amyloid A; −139 versus 0 units for anti-CCP; −6.3 versus 0.0 units for RF–IgM; −4.6 versus 0.0 units for RF–IgG and −3.0 versus 0.0 units for RF–IgA. At week 24, the median change from baseline in immunoglobulin levels for ofatumumab and placebo, respectively, were: −1.30 versus −0.60 g/l for IgG; −0.30 versus −0.02 g/l for IgM and −0.23 versus −0.09 g/l for IgA. A small number of patients on ofatumumab or placebo had immunoglobulins equal to or less than the lower limit of normal during the study (IgM 6 vs 4; IgG 5 vs 1; IgA, no patients, respectively). No patients treated with ofatumumab developed detectable anti-ofatumumab antibodies at week 24.
Safety

The overall incidence of AE was 89% and 55% in ofatumumab and placebo groups, respectively (table 3). Within the ofatumumab group the most commonly reported AE were rash (21%) and urticaria (12%); these events mostly occurred on the day of first infusion (19% and 12%, respectively). The proportion of patients experiencing an infusion-related AE on the day of first infusion was 68% for ofatumumab and 6% for placebo; infusion-related AE on the day of second infusion markedly declined (<1% and 0%, respectively). Most AE were of mild or moderate intensity. Severe AE were reported for 8% of patients on ofatumumab and 2% on placebo, with 5% and less than 1% occurring on the day of first infusion. AE leading to withdrawal were 9% for ofatumumab and less than 1% for placebo. Four SAE (bacterial gastroenteritis, pneumonia, myocardial infarction, ischaemic stroke) were reported for four patients (3%) in the placebo group and seven SAE (angioedema, interstitial lung disease (fatal), synovitis, pulmonary embolism, diarrhoea and pneumonia, pericardial effusion) were reported for six patients (5%) in the ofatumumab group. Two of these SAE (angioedema, pneumonia), both in the ofatumumab group, were considered by the investigator to be related to the investigational product. There was one fatal SAE of interstitial lung disease (fatal), synovitis, pulmonary embolism, diarrhoea and pneumonia, pericardial effusion in the ofatumumab group. One SAE of bacterial gastroenteritis, pneumonia, myocardial infarction, ischaemic stroke in the placebo group and angioedema, interstitial lung disease (fatal, unrelated to ofatumumab), synovitis, pulmonary embolism, diarrhoea and pneumonia, pericardial effusion in the ofatumumab group were reported. Two neoplasms, both prostatic adenoma and benign prostatic hypertrophy were reported. Two neoplasms, both prostatic adenoma and benign prostatic hypertrophy were reported. Two neoplasms, both prostatic adenoma and benign prostatic hypertrophy were reported. Two neoplasms, both prostatic adenoma and benign prostatic hypertrophy were reported.

**DISCUSSION**

The results from the 24-week, placebo-controlled, double-blind phase of this trial confirm the previously reported efficacy of one course of intravenous ofatumumab in active RA. The results from the 24-week, placebo-controlled, double-blind phase of this trial confirm the previously reported efficacy of one course of intravenous ofatumumab in active RA. 11 In addition, this study provides further information on the efficacy of ofatumumab in a well-defined RA patient population with long-standing disease not controlled by standard methotrexate therapy and not previously treated with other available biological DMARD therapies. Ofatumumab, at a dose of 700 mg administered twice, added to a background stable dose of methotrexate therapy, demonstrated a significantly greater ACR20 response at week 24 (primary endpoint) compared with placebo. Significantly greater improvements were observed in key secondary endpoints such as ACR50, ACR70, change from baseline in both DAS28–CRP and DAS28–ESR, EULAR response, physical function (HAQ–DI) and fatigue (FACIT–F).

Efficacy data from seronegative patients with anti-CPP, as observed in the study, should be interpreted with caution because of the small sample size. Data from a number of clinical trials with rituximab in a range of RA populations seem to be consistent with the findings of this study. The results from the 24-week, placebo-controlled, double-blind phase of this trial confirm the previously reported efficacy of one course of intravenous ofatumumab in active RA. 11
Ofatumumab is a fully human mAb, thereby offering a low immunogenicity potential. Although all patients in the study were on methotrexate, which may suppress the development of antidrug antibodies, and patients only received one course of treatment over 24 weeks, no anti-ofatumumab antibodies were detectable in any of the treated patients. In contrast, 7.9% and 5.4% of RA patients who received the chimeric mAb rituximab 500 mg administered twice and 1000 mg administered twice, respectively, in a study of a similar patient population, developed human antichimeric antibodies at 24 weeks. Overall, 11% of patients with RA have tested positive for auto-antibodies at any time after receiving rituximab. There was no reported correlation between the development of these human antichimeric antibodies and safety or efficacy; nevertheless, the possibility of loss or reduction of efficacy, local reactions, serum sickness/immune complex-mediated disease and major allergic reactions (eg, urticaria, bronchospasm, bronchoconstrictions) is well recognised.

In addition to its efficacy in RA demonstrated in this trial, ofatumumab is approved for the treatment of refractory chronic lymphocytic leukaemia. The mechanism of B-cell tumour lysis is probably through the activation of both complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Compared with rituximab, ofatumumab demonstrates increased binding of C1q and more potent complement-dependent cytotoxicity, even in chronic lymphocytic leukaemia cells with low CD20 expression levels. It is unknown at this time, however, whether these mechanistic differences can translate to improved safety, tolerability, efficacy, or potency over rituximab.

In summary, ofatumumab is a fully human mAb binding an epitope of CD20 distinct to that recognised by rituximab. A single course of two infusions of 700 mg was efficacious and safe in biological-naïve, active RA patients on background methotrexate up to 24 weeks after treatment. As expected for a fully human mAb, ofatumumab did not induce immunogenicity.


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Competing interests Genmab and GlaxoSmithKline provided financial support to the institutions that participated in this study. PCT has received research grants from Merck, UDB, AstraZeneca, GlaxoSmithKline and Roche and has been an invited speaker and advisor for Abbott, Bristol-Myers Squibb, Centocor, Roche, Schering-Plough, Wyeth (acquired by Pfizer in October 2009), Genmab,

Figure 3 Mean change from baseline for DAS28 using CRP over time. CRP, C-reactive protein; DAS28, disease activity score based on 28 joints.
GlaxoSmithKline and UCB. EQ, SM, RK and DJC are employees of GlaxoSmithKline and own stock in GlaxoSmithKline. JG was formerly employed at Genmab and owned Genmab stocks.

Patient consent. Obtained.

Contributors. Helle Kentsgaard and Soren Tamer (Genmab) provided advice on study design. Peter Critchley, Shilpa Vadher and Janet Perkins (GlaxoSmithKline) provided clinical operations, data management and programming support. EQ (GlaxoSmithKline), clinical investigation leader and medical monitor of this trial, authored the manuscript. Editorial support (writing assistance, assembling tables and figures, collating author comments, grammatical editing, and referencing) was provided by Julie Taylor of Peak Biomedical Ltd, Macclesfield, UK and was funded by GlaxoSmithKline.

Ethics approval. All participating sites received approval from national, regional, or investigational centre ethics committee or institutional review boards, as appropriate.

Provenance and peer review. Not commissioned; externally peer reviewed.

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