

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Managed access agreement

**Belimumab (Benlysta) for treating active
autoantibody-positive systemic lupus
erythematosus (SLE)**

Date of agreement	
GlaxoSmithKline UK Limited	Signed Ms Nikki Yates General Manager, GSK UK Limited
Lupus UK	Signed Mr Chris Maker CEO Lupus UK
The University of Manchester (acting through Professor Ian Bruce of the British Isles Lupus Assessment Group Biologics Register [BILAG BR])	Signed The University of Manchester
NICE	Signed Sir Andrew Dillon

<p>NHS England</p>	<p>Signed</p> <p>.....</p> <p>Mr Paul Baumann National Finance Director, NHSE</p>
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1 Purpose of agreement

- 1.1 The purpose of this managed access agreement (agreement or MAA) is to describe the arrangements and responsibilities for the further research/data collection for belimumab (Benlysta) for treating active autoantibody-positive systemic lupus erythematosus (SLE). A positive recommendation within the context of an agreement has been decided by the NICE appraisal committee.
- 1.2 A commercial-in-confidence ancillary agreement containing certain terms relating to the supply of belimumab agreed between the licensed owner of belimumab, GlaxoSmithKline UK Limited, the market authorisation holder (MAH) and NHS England is appended to this agreement at appendix B.

2 Background

- 2.1 When the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, NICE's [guide to the methods of technology appraisal](#) (section 6.4) states that the appraisal committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted.
- 2.2 After considering the advice in the [guide to the methods of technology appraisal](#) the appraisal committee concluded that belimumab was an appropriate technology for a positive

recommendation with research, given within the context of a managed access agreement.

2.3 The appraisal committee recommended that this agreement should include the following key aspects:

- The person having the treatment joins the University of Manchester's British Isles Lupus Assessment Group (BILAG) registry to allow data collection.
- The overall cost of funding belimumab during data collection and re-appraisal compared with current alternative options (including biological treatments) is acceptable to NHS England.
- An exit strategy is agreed, which is acceptable to NHS England, to ensure high-quality care continues for people who had access to belimumab in the NHS if they are no longer eligible for treatment with belimumab after the guidance has been reviewed.

3 Commencement and period of agreement

3.1 This agreement shall take effect on the date of publication of the MAA for belimumab on the NICE website. The start of the research period will occur when funding for belimumab is made available by NHS England, expected no later than the end of September 2016. Subject to clause 3.2, it will remain in force until the earlier of: (i) publication of review of the NICE [guidance for belimumab](#) (TA397); (ii) or until conclusion of the exit strategy (see section 9), should NICE no longer recommend belimumab after their review of the guidance.

3.2 For the purposes of this and subsequent clauses, guidance means the guidance published by NICE in June 2016 in relation to the use of belimumab. The NICE review of the [guidance for belimumab](#) is expected to start upon completion of the BILAG data analysis, which is anticipated to be during year 4 of the BILAG registry

research project. For the avoidance of doubt, this agreement shall expire automatically on the fourth anniversary of when belimumab is first prescribed to a patient through this agreement if it has not expired earlier as a result of publication of the review of the [guidance for belimumab](#). The MAH will provide the relevant data required for the review of the guidance on the product performance and NICE will reissue guidance to the NHS in England based on a review of the data during the fourth year of this agreement.

- 3.3 This agreement shall terminate automatically on the termination or expiry of the commercial agreement relating to the funding of belimumab and entered into between the MAH and NHS England.

4 Patient eligibility

- 4.1 The eligible patient population for treatment with belimumab is as follows:
- 4.1.1 A subgroup of SLE patients with high disease activity (low complement and anti-dsDNA and a SELENA-SLEDAI [SS] score of ≥ 10) despite standard treatment.
- 4.1.2 Treatment with belimumab will be continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.
- 4.1.3 All patients eligible for belimumab will sign a patient consent form to show that they understand and accept the terms of this agreement, which includes what will happen to their treatment with belimumab should NICE guidance change in the future (appendix A).
- 4.2 In order to contain NHS costs during the research, NHS England will fund a maximum of 300 eligible patients in England. An eligible

patient is one that has satisfied the criterion for treatment continuation after 6 months of initial treatment as detailed in section 4.1.2. As soon as 300 eligible patients have been recruited into the registry research study, all centres will be informed that they cannot prescribe belimumab to any new patients for the purposes of this research until NICE has published its guidance review.

5 Research/data collection

5.1 Subject to the University of Manchester and the MAH agreeing funding and other contractual arrangements as mentioned under section 8.3 of this agreement, the University of Manchester will agree to collect the following data as part of the register for patients who have belimumab:

- Demographics (age, sex, ethnicity).
- Comorbidities.
- Belimumab treatment details: date started/stopped/restarted, dose and intravenous frequency, reason for discontinuation (as appropriate).
- Other concomitant and prior treatments for SLE.
- Steroid use: dates started/stopped for each dose change.
- Clinical response: SLEDAI 2K and BILAG Index 2004 at start, after 3, 6 and 12 months and annually thereafter.
- Organ damage accrual: SLICC Damage Index and BILAG Index 2004 at start and 3, 6, 12 months and annually thereafter.
- Clinical serology – autoantibody profiles.
- Serious adverse events (SAEs): that is, death, hospitalisation for infection, malignancy, other SAEs, as agreed with BILAG in accordance with the MAH governance requirements for adverse event reporting to regulatory authorities.

- Patient reported outcomes: LupusQoL, SF-36, EQ-5D at 0, 6, 12, 18 and 24 months and annually thereafter.
- Patient diary records (hospital admissions, visits to outpatients and medications).
- Lifestyle questionnaire (for example drinking, smoking, employment status).

5.2 The key data collected comprising treatment duration, steroid dose reductions, change in SLEDAI score over time and patient reported outcomes (EQ-5D, SF-36 and LupusQoL) will be used to inform the cost-effectiveness analyses during guidance review.

6 Control of the data

6.1 The University of Manchester, acting through the BILAG steering committee, will control and own the data collected in the registry for belimumab. The research will be led by Professor Ian Bruce, Arthritis Research UK Epidemiology Unit and The Kellgren Centre for Rheumatology, at The University of Manchester.

7 Data analysis

7.1 The University of Manchester will provide a summary of patient recruitment into the registry to NHS England and the MAH after every 3 months in order to monitor recruitment rate.

7.2 The University of Manchester, the MAH or an approved third party, agreed with the University of Manchester, will analyse the registry data at the end of the data collection period in order to meet the timing requirements of the NICE review. Analyses will be conducted in accordance with a pre-defined analysis plan agreed between the MAH and the University of Manchester (further details provided in a separate contract between the MAH and the University of Manchester). The MAH will generate the appropriate cost-effectiveness analyses and report to submit to a NICE

technology appraisal as soon as possible after data analysis completion.

- 7.3 If required, the University of Manchester will provide the MAH with a dataset of anonymised patient level data to enable additional analyses for the health economic assessment to be conducted.

8 Funding

- 8.1 During the period of data collection and the period of re-appraisal, the MAH will provide belimumab to the NHS with the discount agreed in the approved patient access scheme.
- 8.2 NHS England will fund the belimumab costs during the period of data collection and the period of re-appraisal for 300 eligible patients up to the expiry date of this agreement. In order to share the risk of funding a treatment that may ultimately prove not to be cost effective, a commercial-in-confidence ancillary agreement containing certain terms relating to the supply of belimumab agreed between the MAH and NHS England is appended to this agreement at appendix B.
- 8.3 The MAH will provide the agreed annual funding to the University of Manchester (as detailed in a separate contract between MAH and the University of Manchester) to cover the costs of data collection over the agreed period of research.
- 8.4 The MAH will fund the University of Manchester, or a third party (as appropriate) to conduct the required analyses at the end of the research data collection period, or alternatively will undertake the analysis itself.

9 Exit strategy

- 9.1 If at the end of the four-year agreement, NICE no longer recommends belimumab for NHS funding, or only recommends

belimumab for a smaller subpopulation of SLE patients than the current guidance, NHS England funding for belimumab will cease to be available for any new or existing patients where there is no longer a recommendation for its use. In which case treatment cessation shall be managed between the MAH, the University of Manchester's BILAG study site centres and NHS England to ensure it is effected in a controlled manner (detailed in the confidential ancillary agreement in appendix B).

- 9.2 The cessation of funding under this agreement and the conditionality of further funding as specified in clause 9.1 above apply notwithstanding any desire which patients and their NHS clinicians may have for continued treatment with belimumab. NHS England, the University of Manchester and the MAH shall use their reasonable endeavours to ensure that any patient being treated with belimumab which is funded by NHS England under this agreement is made aware of these funding limitations and accepts them when they sign the patient consent form.
- 9.3 If NICE guidance has not been issued by the end of the fourth year of this agreement and the review is unlikely to reach a conclusion soon thereafter, if there is no new agreement in place to continue funding Belimumab then either the MAH or NHS England has the right to request that the exit strategy is initiated.

10 Ongoing review of this agreement

- 10.1 Representatives from NHS England, the University of Manchester, the MAH and NICE will meet biannually to consider how the registry research is progressing.

11 Counterparts

- 11.1 This agreement may be executed in any number of counterparts, each of which when executed and delivered shall constitute a

duplicate original, but all the counterparts together shall constitute one agreement.

11.2 Transmission of the executed signature page of a counterpart of this agreement by email (in PDF, JPEG or other agreed format) shall take effect as delivery of an executed counterpart of this agreement.

11.3 No counterpart shall be effective until each party has executed and delivered at least one counterpart.

12 Publication

12.1 The process for any publications arising from this research will be jointly agreed and authored by the University of Manchester and the MAH, subject to the more detailed publication process being agreed and outlined in the separate agreement as mentioned under section 8.3 of this agreement.

13 Limitation of liability

13.1 The liability of the University of Manchester for any breach of this agreement or arising in any other way out of the service or subject-matter of this agreement, will not extend to any punitive, exemplary, special, incidental or consequential damages or losses including (without limitation) loss of profits. Except where limitation of liability is not permitted by statute, the aggregate liability of the University of Manchester (whether in contract or for negligence or breach of statutory duty or otherwise howsoever) to other parties for any loss or damage of whatever nature and howsoever caused shall be limited to and in no circumstance shall exceed the total funding received by the University of Manchester from the MAH, as outlined in section 8.3 of this agreement.

14 Governing law and jurisdiction

- 14.1 This agreement will be governed by and will be construed in accordance with the laws of England and Wales, without regard to principles of conflicts of laws applicable in such jurisdiction and not in accordance with the laws of any other jurisdiction. Any dispute under this agreement shall be decided in the courts within England.

Appendix A

Information to patients regarding the use of belimumab ▼ (Benlysta) under current NICE Guidance and an NHS England agreed MAA

NICE has issued positive guidance for belimumab (Benlysta) on the condition that data will be collected from patients with lupus eligible to receive belimumab for an initial period of up to 3 years. These data will be stored in a UK British Isles Lupus Assessment Group (BILAG) registry as part of a research study in which the drug will be funded by NHS England. After this initial period of data collection the data will be analysed and provided to NICE for a re-assessment of the efficacy and cost effectiveness of belimumab. This current NICE recommendation is conditional on what is known as a managed access agreement (MAA). This agreement has involved extensive discussion between NHS England, BILAG, GlaxoSmithKline (the marketing authorisation holder or MAH), Lupus UK and NICE. All these parties have signed to confirm that the agreed terms of the MAA will be followed.

The MAA requires:

- Assurance from the MAH that it will collaborate with the BILAG and NHS England to collect your anonymised data and will help fund the BILAG registry.
- Agreement between the MAH and NHS England to manage the total costs of belimumab to the NHS during the data collection, data analysis and NICE review periods.

During year 4 of the research a review by NICE will look at the new data collected for belimumab. NHS funding beyond this point will depend on the outcome of this further NICE review. The MAA (and therefore agreed funding for belimumab) expires 4 years after the start of the registry research study for belimumab (expected around October 2020), or following an earlier review should this be required.

Patient eligibility

1. It has been agreed that the patient population with SLE who are eligible to take part in this research will be a subgroup of SLE patients. This subgroup must have high disease activity with SLE still uncontrolled after treatment with other medications commonly prescribed for SLE. This subgroup of patients is defined in the NICE guidance.
2. Only patients who have a certain level of improvement satisfying what is called a continuation rule after 6 months of treatment will be eligible to continue belimumab beyond this time point. This rule requires a clinical assessment by your clinician on how well the disease has been controlled by the medicine.
3. Belimumab will not be started if any of the following apply:
 - The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long-term benefit, for example cancer or multiple sclerosis.
 - The patient is unable or unwilling to comply with the associated monitoring criteria.

What happens after the NICE review of the new research evidence?

- If, after the next NICE guidance review, the recommendation remains positive then NHS England will continue to fund belimumab for those patients with lupus who meet the NICE recommendations for the medicine. Under these circumstances you may continue with belimumab if your clinician believes it continues to provide benefit to you and this is what you wish
- However, if after the guidance review, NICE no longer recommends belimumab for any patients who have lupus then:
 - No new patients with lupus will be offered belimumab on the NHS.
 - If you are receiving belimumab at this time, you will need to be transitioned off this medicine on to other treatments for SLE during the

following year. Your clinician will ensure that this is done in a safe way for you. **Please be aware that this will be required even if you and your clinician have seen a benefit to you from belimumab.**

If NICE recommends belimumab for a different subpopulation of lupus patients with clinical criteria other than those currently defined in its current guidance (TA397) then NHS England will continue to fund any new and ongoing lupus patients who have these particular clinical criteria. Any other patients with lupus receiving belimumab at that time and who fall outside this revised subpopulation will also need to be transitioned off belimumab on to alternative therapies during the year following the revised NICE guidance publication. **Please be aware that this will be required even if you and your clinician have seen a benefit to you from belimumab.**

It is important that you understand and agree to accept the uncertainties outlined above. We know that this is complex and could be confusing to you or your relatives, so please ask for clarification over any details that are still not clear to you.

Belimumab ▼ is subject to additional monitoring requirements by the Medicines and Healthcare products Regulatory Agency (MHRA), the authority that licenses medicines for use in the UK. If you do agree to take part in this research you will be asked to help report any side effects you may get. You can find out other information about this on the MHRA's [Yellow Card Scheme](#) website.

Anonymous data collected will be shared with NICE and the MAH for the purposes of a NICE appraisal review. Research papers and other scientific findings may be developed and published based on information provided in the registry and by signing below, you understand and consent to your data being used for such scientific and academic purposes.

In order to be eligible to start treatment with belimumab you must understand and agree to all of the terms detailed in this information leaflet.

Patient Name: _____ Name of Clinician: _____

Signature: _____ Signature of Clinician: _____

Date: _____ Date: _____

Appendix B

Confidential Ancillary Agreement between GlaxoSmithKline Ltd and NHS England

(The ancillary agreement contains commercial-in-confidence information and has been redacted from the managed access agreement)