NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Addendum to Managed Access Agreement

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

Date of agreement	
GlaxoSmithKline UK Limited	Signed ..... Robert Huxford Specialty Business Unit Head, GSK UK
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 ..... Dr Andrew Walsh Director of Research and Business Engagement, The University of Manchester
NICE	Signed ..... Brad Groves Associate Director, Managed Access, NICE
NHS England	Signed ..... John Stewart National Director, Specialised Commissioning NHSE

1 Purpose of and Background to Addendum Agreement

1.1 The original Managed Access Agreement (MAA), aligned to NICE guidance TA397 for belimumab for the treatment of adult systemic lupus erythematosus (SLE) patients, was published on the NICE website on the 22nd June 2016.

1.2 The purpose of this MAA addendum is to permit the inclusion of paediatric SLE (pSLE) patients (aged 5 to 17 years), who satisfy the current NICE reimbursed population, to be treated with belimumab and included in the BILAG registry. This will allow their data to be included in the data analysis which will form part of the NICE guidance review of belimumab (Benlysta).

2 Commencement and period of addendum

2.1 This MAA addendum shall take effect from the date of full sign-off of this document and after market authorisation of the belimumab paediatric license extension has been obtained. Subject to clause 3.2 in the MAA, it will remain in force until the earlier of: (i) publication of NICE final guidance for belimumab (TA397); (ii) or until conclusion of the exit strategy (see section 9 of the MAA), should NICE no longer recommend belimumab after their review of the guidance.

3 Patient eligibility

3.1 The eligible patient population for treatment with belimumab will be identical to that detailed for the adults in the MAA and is as follows:

3.1.1 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.

3.1.2 Treatment with belimumab will be continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.

3.1.3 All parents/guardians of patients eligible for belimumab and aged less than 16 years will sign a consent form to show that they understand and accept the terms of the MAA agreement, which includes what will happen to their

child's treatment with belimumab should NICE guidance change in the future). In addition, all children up to the age of 16 years will sign an assent form with the help of theIr parents, if appropriate. Once a patient reaches the age of 16 years, they will be asked to sign the adult patient consent form (see appendix A of the original MAA).

4 Research/data collection, Control of the data, Data analysis, Funding and Exit strategy

The processes and terms will be identical to those detailed in Sections 4 to 8 in the MAA except for the collection of Patient Reported Outcomes (PROs). The LUPUSQoL instrument is not collected/validated in less than 18 year olds. For the main BILAG-BR SLE study children are asked to complete the EQ-5D, the Childhood Health Assessment Questionnaire (CHAQ), and the Child Health Utility 9D (CHU9D) instruments.

5 Counterparts

5.1 This agreement addendum 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 addendum.

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

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

Appendix A.1

Additional Parent/Guardian Leaflet for consent on behalf of their child

Title of Project: Effectiveness of belimumab (Benlysta) in SLE (lupus) as prescribed in UK clinical practice

The National Institute for Health and Care Excellence (NICE) has recommended NHS funded treatment with belimumab (also known as Benlysta) for an initial period of up to 4 years for patients who have been diagnosed with Lupus and who meet the starting rules outlined in a Managed Access Agreement **(MAA).** A MAA is a way that doctors and the NHS can assess the long-term benefits of a new medicine by collecting agreed test results over a given period of time in patients who have certain symptoms of a condition. This MAA 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.

Patient eligibility and rules for continuation of treatment

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 and data collection.

Data collection

A condition of the MAA is that patients who receive treatment with belimumab have their data collected to help inform future NHS funding decisions.

The table below details the assessments that will be made on your child. Your doctor can explain what these are.

	Time post therapy					
Data	**Baseline**	**3 mths**	**6 mths**	**12 mths**	**24 mths**	**36 mths**
Consent/Assent	✓					
Clinical assessment	✓	✓	✓	✓	✓	✓
Co-morbidities	✓					
Concomitant medications	✓	✓	✓	✓	✓	✓
Adverse Events	✓	✓	✓	✓	✓	✓
SLE details:						
BILAG INDEX 2004	✓	✓	✓	✓	✓	✓
SLEDAI-2K	✓	✓	✓	✓	✓	✓
SLICC Damage Index	✓			✓	✓	✓
Prior therapy	✓					
Patient Questionnaire						
EuroQol / EQ-5D	✓	✓	✓	✓	✓	✓
CHAQ[#]	✓	✓	✓	✓	✓	✓
CHU9D[##]	✓	✓	✓	✓	✓	✓
Patient diary	✓	✓	✓	✓	✓	✓
Bloods (drawn at routine monitoring time points only)						
Basic laboratory values, e.g. Auto antibody profiles, Complement fractions, Total cholesterol HDL, Fasting blood glucose; ESR/CRP;Immunoglobulins; Serology	✓					
DNA	✓					
mRNA	✓		✓			
Plasma	✓	✓	✓	✓		
Serum	✓	✓	✓	✓		
Urine (from routinely collected samples)	✓	✓	✓	✓		

[#]CHAQ: Childhood Health Assessment Questionnaire; [##]CHU9D: Child Health Utility 9D

These data will be collected by your medical team and stored in an UK British Isles Lupus Assessment Group (BILAG) registry. The data will be analysed by the University of Manchester and GSK before it is provided to NICE for a re-assessment of the efficacy and cost effectiveness of belimumab. All data collected for the purpose of the MAA shall be stored and processed in accordance with all applicable data protection laws.

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. Data that is anonymised cannot be linked back to you and has all personal identification removed.
- 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 (from the date of the original MAA) 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 (dependent of patient recruitment and agreement with NHS England).

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 your child is 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 your child.

Please be aware that this will be required even if you and your clinician have seen a benefit to your child from belimumab.

If NICE recommends belimumab for a different subpopulation of lupus patients with clinical eligibility 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 your child 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 your medical team 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 your child may get. You can find out other information about this on the MHRA's Yellow Card Scheme website.

Your anonymised data collected as part of this agreement 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 child's 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.

If you feel that you and/or your child will be able to comply with the above, please fill in your details below and sign for reimbursed treatment to begin.

Patient Name: _____

Parent/Guardian Name:_____

Signature: _____

Date: _____

Name of Clinician:_____

Signature of Clinician: _____

Date: _____

Appendix A.2

The BILAG Benlysta Prospective Cohort
Information for children and young people

Version 1, 30/10/19

We want to invite you to take part in a research study. Before you decide, it is important for you to understand what it is and what happens. Please read this leaflet carefully and talk to other people about it if you want. Ask us if you don't understand anything. Take time to think it over.

What is the study for?

A new medicine, called Benlysta, which is a type of biological therapy, is being used to treat people with lupus.

We would like to know more about how well this medicine works, how it makes you feel and how you cope with your day to day activities. We will also check that you do not have any bad effects when you take this medicine. A group of doctors, nurses and other people caring for people with lupus have set up a list on a computer to collect this information about people like you with lupus. We would also like to know how you are over the next year or so.

Why have I been chosen?

You have been chosen to be invited because you have lupus and Benlysta is a medicine that could help your illness.

What information will we collect from you?

- The study will collect information about you, your lupus, and medical treatment and how well you are. Information about your health and treatment will be sent to the study for at least one year.
- We would like to collect an extra blood sample from you for the study at a number of different times. We will collect this blood at the same time as your usual blood tests. We would also like to collect a small sample of urine from you.
- We would like you to fill in some questionnaires about how you feel and let us know in a diary any time you go to hospital or have new medicines. If you want someone to help with this that is fine.
- We hope the research will help doctors to treat patients better in the future.
- We will also make sure that we can trace you through your family doctor (GP) so we can find out how you are in the future.
- If you or your parents have a complaint about this research study, you can complain to University Research Practice and Governance Coordinator on 0161 2757583 or 2758093 or by email to research-governance@manchester.ac.uk . Please talk to someone at your local centre if you feel you can.

What do I have to do to take part?

Your doctor will ask you if you want to take part in the study. They will answer any questions you have. If you need more time to think about it, please let them know and they will be happy to talk about it at your next appointment. If you want to take part in the study you and your parent will be asked to sign a form to show that you agree. You can change your mind at any time without saying why. Whatever you decide will not change how doctors treat you.

Do I have to take part?

You don't have to take part, it is up to you. If you decide to take part you and your parents will be asked to sign a form saying you agree to take part. If at any time you don't want to do the research any more, just tell your parents, doctor or nurse. They will not be cross with you.

The information collected will be kept a secret. We will keep your name locked away in the study office to help check information, but will not put your name on a computer.

The results of the research will be written about in a medical journal, but not for a few years. Your doctor will be able to tell you how the research is going. No-one will know that your information is included in the research.

If you would like to know more you can ask one of the doctors or nurses looking after you or you can contact Professor Ian Bruce at the University of Manchester:

0161 2755993
ian.bruce@manchester.ac.uk

The study will be run by the British Isles Lupus Assessment Group and the Arthritis Research UK Epidemiology Unit at the University of Manchester. Your hospital department will get a little bit of money to help pay for the time your doctor takes to fill in the information about you.

Thank you for helping with this study. If you decide to take part in the study please keep this information sheet so that you can look at it in the future

Appendix A.3

PARTICIPANT ASSENT FORM
Title of Project: Effectiveness of belimumab (Benlysta) in SLE (lupus) as prescribed in UK clinical practice

Name of Researchers: Professor Ian Bruce

Please tick the box if you agree and leave it blank if you don't agree

1.	I have read the information sheet dated 30/10/2019 (version 1) for the study	☐
2.	I understand what the study is about	☐
3.	I have had my questions answered in a way I understand	☐
4.	I know it is up to me to decide to take part. I can change my mind if I want without saying why. My doctors and nurses will still look after me.	☐
5.	I have told the person named below that I agree to take part in the study	☐
6.	I agree that my doctor can provide the researchers with information from my medical notes but they will keep this private.	☐
7.	I agree that my blood can be used for the research study	☐
8.	I agree my urine can be used for the research study	☐
9.	I agree that the study team can share my blood samples with other people doing research for lupus	☐
10.	I understand that my blood samples will be kept safely at the University of Manchester for use in future studies.	☐
11.	I understand that if I change my mind and withdraw consent from this study at a later date, my samples that have been donated cannot be withdrawn or destroyed.	☐
12.	I agree to allow the researcher to make contact with me about other studies in the future	☐
13.	I agree to take part in this study	☐
14.	I agree for my doctor to be told about my participation in the study	☐

Name of person with parental responsibility for child	Date	Signature
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Name of patient	Date	Signature
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Name of person taking consent	Date	Signature
----------	----------	----------
Researcher	Date	Signature
----------	----------	----------

1 copy for patient and person with parental responsibility; 1copy for researcher; 1 copy to be kept with hospital notes