Study Protocol

RITPBC

B-Cell Depleting Therapy (Rituximab) as a Treatment for Fatigue in Primary Biliary Cirrhosis

Version 9.1, 10 November 2015

Newcastle University

NHS National Institute for Health Research

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Sponsored by :	The Newcastle upon Tyne Hospitals NHS Foundation Trust

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2. Protocol signature page

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Signature …… Date ……

Denise Howel, Statistician

Signature …… Date ……

Dr Jennifer Wilkinson, Senior Trial Manager

Principal/Chief Investigator signature

I confirm that I have read and understood protocol version 9.1, dated 10 November 2015. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date ……

Print Name ……

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4. Glossary of Abbreviations

Abbreviation	Definition
ADRs	Serious Adverse Drug Reactions
AE	Adverse Event
ALT	Alanine Transaminase
AMA	Anti-PDH Antibody
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
AUC	Area Under the Curve
BCR	B-Cell Receptor
CIOMS	Council for International Organisations of Medical Sciences
CLL	Chronic Lymphocytic Leukaemia
COGFAIL	Cognitive Failure Questionnaire
CRF	Case Report Form
CRP	C-reactive Protein
CTA	Clinical Trial Authorisation
DMEC	Data Monitoring and Ethics Committee
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EME	Efficacy and Mechanism Evaluation Programme
EOW	Every Other Week
ESS	Epworth Sleepiness Scale
FACS	Fluorescence-activated cell analysis
FBC	Full Blood Count
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
GGT	Gamma-glutamyl transpeptidase

h	Hour
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hb	Haemoglobin
HDL	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
IV	Intravenous
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IPTG	Isopropyl-beta-D-thiogalactopyranoside
IRR	Infusion-Related Reaction
IUD	Intrauterine Device
IUS	Intrauterine System
LFT	Liver Function Tests
MA	Marketing Authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
MR	Magnetic Resonance
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MVC	maximal voluntary contraction
NAD	Nicotinamide Adenine Dinucleotide
NCRF	Newcastle Clinical Research Facility
NCTU	Newcastle Clinical Trials Unit
NHL	Non-Hodgkins Lymphoma
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NMRC	Newcastle Magnetic Resonance Centre
NSAIDS	Non-steroidal Anti-inflammatory Drug

NUTH	The Newcastle upon Tyne Hospitals NHS Foundation Trust
NYHA	New York Heart Association
OGS	Orthostatic Grading Scale
PBC	Primary Biliary Cirrhosis
PDH	Pyruvate Dehydrogenase
RPE	R-phycoerythrin
PI	Principal Investigator
PICs	Participant Identification Centres
PML	Progressive Multi-focal Leukoencephalopathy
PROMIS HAQ	Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire
QoL	Quality of Life
RA	Rheumatoid Arthritis
RPE	R-phycoerythrin
rpm	Revolutions per minute
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UDCA	Ursodeoxycholic Acid
U&Es	Urea & Electrolytes
ULN	Upper Limit of Normal

5. Responsibilities

Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study.

Funder: MRC and NIHR Efficacy and Mechanism Evaluation Programme - EME 10 90 03, and DoH subvention grant are funding this study.

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the study. The day-to-day management of the study will be co-ordinated by the Chief Investigator.

Chief Investigator: This is a single-centre study and the Chief Investigator will have overall responsibility for the conduct of the study at this site.

Trial Management:

The following functions falling under the responsibility of the sponsor will be delegated to Professor David Jones (Chief Investigator):

- Authorisation and Ethics Committee Opinion (including MHRA CTA request, Research Ethics Committee opinion, notification of protocol amendments and end of study, site specific assessment and local Research and Development approval)
- Good Clinical Practice and Trial Conduct (including GCP arrangements, management of IMP, data monitoring, emergency and safety procedures)
- Pharmacovigilance (including defining and recording adverse events/reactions, reporting SUSARs, ensuring SAEs are reviewed by an appropriate committee for safety monitoring, annual listings and safety report)
- Administration of funding for the study

Trial conduct at site

Investigator responsibilities:

- Study conduct and the welfare of study subjects
- Familiarity with the use of the investigational medicinal product as described in the product information, appropriate storage and administration according to the protocol and drug accountability
- Ensuring investigational medicinal product is not used for any purposes other than the conduct of the study
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events
- Screening and recruitment of subjects
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the study
- Provision of adequate medical care in the event of an adverse event

- Obtaining local approval and abiding by the policies of Research Governance. Assistance will be provided by Newcastle Clinical Trials Unit
- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, and any national legislation implementing the EU Clinical Trials Directive (2001/20/EC) and subsequent amendments
- Ensuring that no participant is recruited into the study until all relevant regulatory permissions and approvals have been obtained
- Obtaining written informed consent from participants prior to any study specific procedures
- The Chief Investigator (CI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the study. He shall provide a current signed and dated curriculum vitae as evidence for the Trial Master File
- Ensuring Study Site team members are appropriately qualified by education, training and experience to undertake the conduct of the study
- Availability for Investigator meetings, monitoring visits and in the case of an audit
- Maintaining study documentation and compliance with reporting requests
- Maintaining a site file, including copies of study approval, list of subjects and their signed informed consent forms
- Documenting appropriate delegation of tasks to study personnel e.g. Pharmacist, Research Nurse, Investigator(s)
- Ensuring data collected is accurate, timely and complete
- Providing updates on the progress of the study
- Ensuring subject confidentiality is maintained during the project and archival period
- Ensuring archival of study documentation for a minimum of 15 years following the end of the study

6. Protocol Summary

Short title:	RITPBC
Protocol version:	9.1
Protocol date:	10 November 2015
Chief Investigator:	Professor David Jones
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funders:	MRC and the NIHR Efficacy and Mechanism Evaluation Programme - EME 10 90 03 and DoH subvention grant
Study design:	This is a phase II, single-centre, randomised controlled, double blinded trial comparing Rituximab with placebo in fatigued Primary Biliary Cirrhosis patients over 12 months
Study Intervention:	Rituximab v placebo
Primary objective:	To compare the efficacy of B-cell depleting therapy in Primary Biliary Cirrhosis patients over 12 months
Secondary objectives:	• To prospectively evaluate the efficacy and influence of Rituximab upon muscle bioenergetics in Primary Biliary Cirrhosis • To identify whether improvements in fatigue in Primary Biliary Cirrhosis associate with changes in muscle bioenergetics and /or physical activity levels
Primary outcome:	Fatigue severity in PBC patients assessed using the fatigue domain score of the PBC-40, a fully validated, psychometrically robust, disease specific quality of life measure (PBC-40 fatigue domain score >33 at study outset)
Number of study sites:	1
Study population/size:	58
Study duration:	3 years 6 months

7. Background

Primary Biliary Cirrhosis (PBC) is a liver disease that predominantly affects females, can present for the first time at any age, and which develops over many years. It is caused by the immune system attacking the body's own tissues. People with PBC frequently experience profound fatigue or tiredness which they liken to their "batteries running down", and although people still want to undertake normal activities they simply lack the energy to be able to do them. This reduces quality of life, makes it difficult for people to work, and can end up with them becoming isolated in the community. At present we have no treatment for fatigue in PBC. Finding a treatment for fatigue in PBC is one of the highest research priorities identified by patient groups.

We have shown that PBC patients with fatigue have an abnormality in the way they generate energy within their muscles. This appears to be associated with the presence of an antibody in the blood which is directed against an important protein which normal cells in the body use to generate energy. In recent years new drug treatments have been developed which allow us to safely suppress the part of the immune system which produces antibodies of the type that seem to cause energy production problems in PBC. As yet, however, the extent to which these medicines can improve fatigue through removal of antibodies in PBC has not been tested.

The aim of this study is to undertake a clinical trial to examine the effects of this treatment ("Rituximab") on severe fatigue in PBC to help us understand whether this will be a potentially useful treatment. This will give us information about how energy generation changes in patients with PBC with and without the treatment and will also help us to develop new treatments for fatigue in other diseases. The study has the potential to improve the quality of life of many patients with PBC, for whom there is currently no hope of improvement.

We will perform a randomised controlled trial of Rituximab therapy in PBC compared to placebo with the primary end point of fatigue severity. The study will be performed in a specialised PBC clinical centre.

Our hypothesis is that the B-cell-directed immunotherapeutic agent Rituximab will improve fatigue in PBC (an important and disabling symptom) through its effect on B-cells producing antibodies which inhibit the function of pyruvate dehydrogenase (PDH) an important energy generating enzyme.

7.1 Justification for patient population

Fatigue is a common and debilitating symptom which frequently impacts significantly on quality of life and ability to function in patients with PBC[1]. There are currently no effective treatments for fatigue in PBC and new approaches are urgently required to address this unmet need. Rituximab, a B-cell depleting agent, holds specific promise (with evidence from a small-scale proof-of-concept pilot trial) as a therapy for fatigue in PBC, given the strong evidence linking the antibody response to PDH in the pathogenesis of fatigue in this disease. We also believe, given the robust diagnostic criteria and the availability of validated clinical tools, that PBC is an important and useful human model in which to study the pathogenesis and treatment of fatigue.

7.2 Current treatment

There are currently no treatments for fatigue in PBC and we are not aware of any other treatments under evaluation.

A pilot study performed in Canada exploring the use of Rituximab in PBC (in 13 patients) has provided proof-of-concept, showing that the agent is safe and well-tolerated in patients, and is associated with a clinically significant reduction in fatigue[2]. Fatigue severity was assessed using the Fatigue Severity Scale (FSS) (potential range 9-63 points) with a fall being seen from pre-treatment (median FSS=36, range 11-59) to post-treatment (median=29, range 12-55). Taking into account the floor value for the FSS, this represents a median fall in fatigue severity over 6 months of 26%. This compares with our own case-control study of fatigue in PBC which suggests that fatigue severity in age and sex matched normal controls is 30% lower than in PBC patients[1] suggesting the potential for Rituximab therapy to return PBC patients to close to normal with regards to their perceived fatigue. However, this pilot study did not attempt to explore the mechanism of the effect, and since it did not use severe fatigue as an inclusion criteria, the extent of possible improvement for such patients is unclear; moreover, the study was not optimised for the study of fatigue (fatigue was a secondary outcome and only some of the patients who participated had fatigue potentially under-estimating the clinical effect). Patients showed a sustained reduction in anti-PDH antibody levels of all isotypes, supporting the concept that Rituximab has a beneficial effect on fatigue through depletion of PDH-reactive antibody.

The importance of severe fatigue in PBC and the current lack of treatments, the strong theoretical basis for the approach, and the supportive pilot trial proof-of-concept data all, we believe, justify a formal clinical trial of Rituximab targeting fatigue in PBC. Data from animal models of PBC implicating activated B-cells in promoting autoreactivity[3], from human *in vitro* studies showing increased TLR-mediated B-cell activation in PBC[4], from human genetic studies showing disease associations with loci implicated in regulation of the B-cell pool size[5] and the pilot trial data showing improvement in liver biochemistry in PBC patients treated with Rituximab all point to the potential for an additional, more generic benefit for this treatment in terms of underlying liver inflammation further justifying a substantive clinical trial in PBC.

7.3 Rationale for intervention

The underpinning mechanistic data support a role for anti-PDH in the pathogenesis of fatigue in PBC, and the pilot trial of Rituximab supports B-cell depletion therapy as a potentially important approach to ameliorating fatigue[2]. There is thus a pressing need to build on these promising studies to confirm or refute a therapeutic benefit for Rituximab for fatigue in a trial optimised for studying a fatigue effect, and to develop more effective ways of using this agent. The proposed randomised phase II clinical trial will determine the efficacy and safety of Rituximab compared to placebo in PBC and explore the underlying mechanisms of action. It is important with subjective symptoms such as fatigue that a placebo arm is included and that the study is double-blinded. We have included mechanistic components to the trial to allow us to understand the physiological changes that happen in individuals in association with changes in the primary endpoint of fatigue severity. This will allow a complete understanding of the changes in symptoms seen in patients, and establish or refute the mechanistic links between anti-PDH, mitochondrial bioenergetic abnormality and clinical fatigue. This will potentially increase our understanding of fatigue pathogenesis and potential approaches to its

treatment of fatigue in PBC and will allow us to ascertain whether the improvements are generalisable to other fatigue associated diseases or are specific to PBC or particular phenotypes.

The primary endpoint is improvement in fatigue severity as assessed using the fatigue domain of the PBC-40, a fully validated, patient-derived disease-specific quality of life measure developed by the applicants[6]. This measure, which has robust psychometric properties, is recognised as the gold-standard symptom assessment tool for PBC[7, 8] and is in routine use in clinical trials in PBC with a Quality of Life (QoL) element. The study has several secondary end-points designed to address:

- The breadth of the clinical effect of Rituximab in PBC, exploring impact on other symptoms, functional status and mood, as well as the nature and severity of underlying liver injury
- The mechanism of action of Rituximab in terms of its effects on anti-PDH antibody of all isotypes and the B-cells producing it and the associated impact on muscle bioenergetic and cardiorespiratory function
- The acceptability of Rituximab therapy for patients in terms of tolerability and safety

7.4 Risks and Benefits of proposed intervention

We believe that the potential benefits of Rituximab for the treatment of severe fatigue in PBC out-weigh any potential risks making the proposed study justifiable.

7.5 Potential benefits: Patients describe fatigue as being the worst aspect of having PBC, frequently making their lives intolerable. They tell us that if we could find a treatment for fatigue they could live with everything else about the disease, including the potential need for transplantation in the future. We believe, based on our mechanistic studies and the pilot trial, that Rituximab has the potential to be a highly effective treatment for fatigue in PBC. The proposed application will also provide evidence for the mechanistic basis for the action of Rituximab providing important insights into the pathogenesis of fatigue in PBC and other chronic disease, potentially opening up important new avenues for the treatment of this pervasive symptom.

7.6 Potential Risks: The potential risks of Rituximab are typical of biological therapies and relate principally to its immuno-suppressive actions. Rituximab has, however, been used extensively and safely in the treatment of autoimmune disease. Experience from the use of Rituximab for the conditions for which it is currently licensed (rheumatoid arthritis (RA), Non-Hodgkins Lymphoma (NHL) and chronic lymphocytic leukaemia (CLL)) suggest that the most frequently observed serious adverse drug reactions (ADRs) are: infusion-related reactions (including cytokine-release syndrome); bacterial and viral infections; and cardiovascular events. Other serious ADRs, but reported less frequently, include progressive multi-focal leukoencephalopathy (PML). These risks are well understood from routine use and clinical trials in other disease areas and there are recommended prophylactic and symptomatic management strategies to deal with them. We recognise that these treatment-related risks may equally apply to PBC patients. We believe, however, that our protocol, and the experience within the Newcastle Clinical Research Facility (CRF) of utilising molecular immuno-modulatory approaches minimises the risks to patients. The CRF has dedicated staff and equipment (including full resuscitation facilities) in place to deal with these risks and ready access to critical care facilities within the same building should the need arise.

There will also be the theoretical potential for PBC-specific risks from effects of Rituximab on the underlying disease process. Importantly, however, no adverse events or short-term disease worsening were reported in the pilot trial of Rituximab[2]. The patients participating in this trial also demonstrated no long-term worsening of disease or specific complications (Mark Swain direct communication). None of the PBC patients receiving Rituximab demonstrated disease worsening of the type recently reported following B-cell depletion in murine xenobiotic sensitisation model proposed, but not widely accepted, as an animal model of PBC[9]. The complete discrepancy in response to B-cell depletion between human PBC patients and this murine model provides, in our view, further support for the argument this is not a valid model of PBC, rather than suggesting that Rituximab therapy holds specific risk. The further, as yet unpublished study of Rituximab in PBC of which we are aware similarly showed improvement rather than worsening of liver function.

The research elements of the study (blood-based assessment and MR scan) present no meaningful risk to the participants.

8. Objectives

Primary objective:
To undertake a phase II clinical intervention study in PBC patients with anti-PDH antibody (this is present in over 90% of patients) and with significant fatigue.

The primary endpoint is severity of fatigue as assessed using PBC-40, a disease-specific quality of life measure and will be evaluated at baseline, 12 weeks, and three monthly thereafter up to 12 months.

Secondary objectives:
To explore the extent to which any such improvement in fatigue is related to reduction in the level of anti-PDH antibody in PBC patients, and any associated affect on biomarkers of bio-energetic function assessed using unique MRI protocols developed by the applicants.

To further explore the safety of Rituximab in PBC and the sustainability of its beneficial actions.

Evaluation of the secondary endpoints will be carried out at baseline and 12 weeks.

9. Study design

This is a phase II, single-centre, randomised controlled, double blinded trial comparing Rituximab with placebo in fatigued Primary Biliary Cirrhosis patients over 12 months.

A total of 58 patients (29 per arm) with PBC and severe fatigue will be recruited and randomised (see section 16 for power calculation).

A qualitative study of the perceived value of biological therapies for the treatment of fatigue and attitudes to potential long term value in terms of fatigue (a life-altering but not life-threatening symptom) versus implications of use of significantly immune-modulatory treatment will also be undertaken to guide any future use of this therapy in practice.

9.1 Primary outcome measure:

The primary outcome variable is fatigue severity in PBC patients, assessed using the fatigue domain of the PBC-40, a fully validated, psychometrically robust, disease specific quality of life measure, between baseline and 12 week assessment (PBC-40 fatigue domain score >33 at outset: A value validated against a control population in a now validated normal population of the PBC-40 (PBC-40n)).

9.2. Secondary outcome measures:

1. Improvement in physical activity assessed using seven day physical activity monitoring (previously shown to be impaired in fatigued PBC patients with degree of impairment shown to associate with perceived fatigue severity).

2. Improvement in daytime somnolence (as assessed using the Epworth Sleepiness Scale[20] (ESS)), vasomotor autonomic symptoms (assessed using the Orthostatic Grading Scale[21] (OGS)), functional status (assessed using Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire[17] (PROMIS HAQ) and the Cognitive Failure questionnaire (COGFAIL[18])). Reduction in depressive and anxiety-related symptoms will be assessed using the Hospital Anxiety and Depression Scale[19] (HADS).

3. Reduction in serum anti-pyruvate dehydrogenase complex antibody levels assessed using ELISA and in numbers of peripheral blood B-cells specific for pyruvate dehydrogenase complex assessed using a novel tetramer-based technology (to confirm whether any clinical effect is directly related to antibody modulation).

4. Improvement in peripheral muscle bio-energetic function on exercise (to confirm whether any clinical effect is directly related to effects on muscle bioenergetic function).

9.3 Definition of end of study:

The end of the study is defined as last patient, last visit (12 month follow-up visit).

10. Subject population

Participants will be patients with definite or probable Primary Biliary Cirrhosis established using recognised epidemiological criteria.

10.1 Inclusion criteria:

- age ≥ 18 years
- patient has capacity and provided written informed consent for participation in the study prior to any study specific procedures
- moderate or severe fatigue as assessed using previously designated cut-offs of the PBC-40 fatigue domain (i.e. fatigue domain score >33)
- presence of AMA (anti-PDH antibody) at a titre of >1:40
- adequate haematological function Hb >9g/L, absolute neutrophil count >1.5x10^9/L, platelet count > 50x10^9/L
- bilirubin ≤ 50 µmol
- INR ≤ 1.5
- Child-Pugh score < 7
- ECOG performance status < 2
- adequate renal function; Cockroft and Gault estimation > 40ml/min
- women of childbearing potential should have a negative pregnancy test prior to study entry AND be using an adequate contraception method, which must be continued for 12 months after completion of treatment. Acceptable forms of effective contraception include:
    - established use of oral, injected or implanted hormonal methods of contraception
    - placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
    - male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
    - true abstinence: when this is in line with the preferred and usual lifestyle of the subject

10.2 Exclusion criteria:

- advanced or decompensated disease (variceal bleed, hepatic encephalopathy or ascites)
- history or presence of other concomitant liver diseases (including hepatitis due to hepatitis B (surface antigen positive or core antibody positive) or C or evidence of chronic viraemia on baseline screening), primary sclerosing cholangitis or biopsy proven non-alcoholic steatohepatitis)
- average alcohol ingestion >21 units/week (male) or >14 units/week (female)
- chronic sepsis or intercurrent condition likely to predispose to chronic sepsis during the study

- previous treatment with B-cell depleting therapy
- previous history of aberrant response or intolerance to immunological agents
- presence of significant untreated intercurrent medical condition itself associated with fatigue
- presence of significant risk of depressive illness (HADS score indicating caseness)
- current statin therapy or statin use within 3 months of enrolment
- ongoing participation in other clinical trials or exposure to any investigational agent 4 weeks prior to baseline or within < 5 half lives of the investigational drug
- major surgery within 4 weeks of study entry
- vaccination within 4 weeks of study entry; patients requiring seasonal flu or travel vaccines will be required to wait a minimum of 4 weeks post vaccination to enrol in the study
- pregnant or lactating women
- psychiatric or other disorder likely to impact on informed consent
- patient is unable and/or unwilling to comply with treatment and study instructions
- any other medical condition that, in the opinion of the investigator would interfere with safe completion of the study
- hypersensitivity to the active substance (Rituximab) or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water (for infusion)) or to murine proteins
- active, severe infections (e.g. tuberculosis, sepsis or opportunistic infections)
- known HIV infection
- clinical history of latent TB infection unless the patient has completed adequate antibiotic prophylaxis
- AST/ALT 4 x upper limit of normal
- severe immune-compromised state
- severe heart failure (NYHA Class IV) or severe uncontrolled cardiac disease
- malignancy (other than basal cell carcinoma) within the last 10 years
- demyelinating disease
- previous participation in this study
- any contraindication to Rituximab therapy not covered by other exclusions

11. Screening, recruitment and consent

11.1 Identification and screening of participants:

- information about the study will be widely disseminated via all relevant patient groups.

- potential participants will be identified through routine clinic outpatient appointments by their treating physician, who is an existing member of their clinical care team (the CI or other members of the research team with documented, delegated responsibility).

- In addition, eligible patients as identified by the CI or other members of research team will be sent Participant Information sheets accompanied by an Expression of Interest Form by post.

- Potential participants will also be identified through Participant Identification Centres (PICs) by their treating physicians. The Expression of Interest Form and the Participant Information Sheet will be given to potential participants at the PICs by their treating physicians.

- Study posters will be placed in the relevant clinics at each site, with contact details of the members of the research team.

- the screening assessments (as per routine clinical practice) must occur within 4 weeks prior to baseline visit.

- Potential participants will also be identified through the UKPBC platform.

11.2 Recruitment procedures

Eligible participants will be invited to participate by the consultant in an outpatient clinic appointment and have the study explained to them. If the patient has not already received the Participant Information Sheet (PIS), it will be provided at this time and the patient allowed to take it away for consideration. Patients will have a minimum of 48 hours to consider the information before written informed consent is obtained.

An eligibility screening form will be completed by the research team to document participants' fulfilment of the entry criteria for all patients considered for the study and subsequently included or excluded. The log will also ensure potential participants are only approached once.

11.3 Consent procedures

Informed consent discussions will be undertaken by appropriate site staff (as per delegation log) involved in the study, including medical staff and research nurses, with opportunity for participants to ask any questions. Following receipt of information about the study, participants will be given reasonable time (at least 48 hours) to decide whether or not they would like to participate. Those wishing to take part will provide written informed consent by signing and dating the study consent form, which will be witnessed and dated by CI or a member of the research team with documented,

delegated responsibility to do so. Written informed consent should always be obtained prior to randomisation and prior to study specific procedures/investigations.

The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. The participant will specifically consent to their GP being informed of their participation in the study.

The right to refuse to participate without giving reasons must be respected.

Due to the small subject population, the information sheet and consent form for the study will be available only in English. Interpreters will be arranged for all visits of patients who require them either for verbal translation of for deaf subjects wishing to take part in the study, via local NHS arrangements. Qualified interpreters will be used to explain the consent form and information sheet, and great priority will be placed on finding the most direct communication.

12. Study medication / Intervention details

12.1 General information

Rituximab is widely used in the UK for Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis even though this is outwith its Marketing Authorisation (MA). For purposes of this study, Rituximab will be treated as an investigational medicinal product (IMP).

For reported side effects of Rituximab please refer to Section 19 Pharmacovigilance.

Rituximab has a shelf life of 30 months. The prepared infusion solution of MabThera® is physically and chemically stable for 24 hours at between 2 °C and 8 °C and subsequently 12 hours at room temperature. Please refer to the Summary of Product Characteristics (appendix 1) for more details.

12.2 Study administration

All Study medication (Rituximab) will be labelled according to the requirements of Annex 13. Study medication is for use by study participants only.

Participants will be randomised to Rituximab therapy (1000 mg IV on days 1 and 15) or placebo (0.9% Sodium Chloride 250mls) control. The Rituximab dosing regimen identified is that used in the proof of concept study, which is also the established treatment regimen for Rituximab use in rheumatoid arthritis. All interventions will be administered with a clinician present throughout the infusion in participants who have been encouraged to have adequate oral hydration in the 24 hours prior to attendance. Resuscitation equipment will be immediately available during the infusion period. Blood pressure, heart rate and temperature will be monitored during the infusion. Participants will continue to be observed in the Clinical Research Facility for at least 1 hour after the infusion.

12.3 Experimental intervention: Rituximab Therapy

The investigational medicinal product used in the clinical trial is Rituximab, 1000mg IV. This product has been granted a marketing authorisation by the European Commission (MA number: EU/1/98/067/002). The licence holder of Mabthera® is Roche. The product is supplied as vials containing 500 mg of Rituximab at a concentration of 10mg/ml. Supplies of Rituximab will be stored in a refrigerator at between 2°C and 8°C, in a secure location in their original packaging in order to protect from light. Supplies of Rituximab will be labelled as IMP in accordance with regulatory requirements. Storage and supply of the Rituximab will be delegated to the Trust pharmacy at the Royal Victoria Infirmary Newcastle. Rituximab will only be released once all the appropriate regulatory and governance approvals are in place. Patients randomised to receive Rituximab therapy will be given treatment at the infusion rates recommended for rheumatoid arthritis patients (i.e. for the first infusion at an initial rate of 50 mg/h; after the first 30 minutes it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. Second and subsequent doses can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h at 30 min intervals to a max of 400mg/h). Please see the Clinical Research Facility Rituximab infusion guideline that is approved by the Newcastle upon Tyne Hospitals NHS Foundation Trust (Appendix 5) for more details.

12.4 Control Intervention: Placebo Infusion

Patients randomised to receive placebo will receive a control normal saline infusion. The control infusion will be delivered in a double-blinded manner to participants using the same placebo as used in rheumatoid arthritis studies under the supervision of a clinician (per the existing Newcastle Clinical Research Facility Rituximab infusion guideline Appendix 5).

Conditioning: In line with recommendations for the administration of Rituximab in other conditions, all patients will receive a conditioning regimen prior to the infusions of study medication on days 1 and 15 to maintain double-blinding. The conditioning regimen will comprise: Paracetamol 1g PO to be administered 1 hour prior to infusion; Chlorphenamine 4mg PO to be administered 1 hour prior to infusion; and Methylprednisolone 100mg IV to be administered 30 minutes prior to infusion. The Paracetamol, Chlorphenamine and Methylprednisolone will be sourced locally. Symptomatic management of adverse reactions may be treated with non-steroidal anti-inflammatory drugs and analgesics as necessary.

It should be noted that there must be an interval of at least two weeks between the two doses of Rituximab on day 1 and day 15. A deviation of + /- 7 days is acceptable between the first and second infusion, however, the two week interval must be maintained.

A two day visit window is allowed for each dispensing visit.

Study medication will be prescribed by a study clinician according to the protocol, and administered to the patient by clinical staff according to local pharmacy policy. All unused study medication will be stored in Pharmacy until the end of the study, or until the trial manager has completed appropriate reconciliation.

Documentation of prescribing, dispensing and return of study medication shall be maintained for study records.

Adverse Reactions during treatment administration: During the infusion patients will be monitored clinically for the onset of clinical features of infusion-related reactions (IRR, the commonest adverse event in Rituximab usage). Patients who develop evidence of severe IRR, especially severe dyspnoea, bronchospasm or hypoxia, will have the infusion interrupted immediately. The infusion will not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time the treatment will be stopped. Mild or moderate IRR will be addressed by halving the rate of infusion. The infusion rate may be increased again upon improvement of symptoms. Paracetamol and/or NSAIDS can be prescribed for the symptomatic management of IRRs.

Concomitant medication

For management of concomitant therapies, please refer to the Rituximab Summary of Product Characteristics (Appendix 1). A complete listing of all concomitant medication received during the treatment phase must be recorded in the relevant CRF.

For patients who are on Ursodeoxycholic Acid (UDCA), the UDCA dose should not be changed during the period of study. No other disease modifying agents should be introduced during the duration of the trial. Therapy aimed at reducing Pruritus and its impact can be introduced if unavoidable at the discretion of the investigators.

Live vaccines must not be given during the study.

13. Randomisation

Randomisation will be conducted by the Newcastle Clinical Trials Unit (NCTU) web based system on a 1:1 ratio and random-permuted blocks with random block length. The treatment allocation will be kept blind from the subjects and the study assessors and investigators until study completion. The randomisation system will generate a treatment arm for each participant that links to the corresponding allocated study drug (blinded). The participant study ID will be clearly documented by the investigator on the trial prescription to ensure the study pharmacist dispenses the correct study medication.

Patients in the study will be randomised to receive either:

- Rituximab therapy on days 1 and 15 - study drug
- Placebo (0.9% Sodium Chloride 250ml) on days 1 and 15 - control

Patients may only be randomised into the study by an authorised member of staff at the study research site, as detailed on the Delegation Log. Patients may only be randomised into the study once.

Contact details for Randomisation: http://apps.ncl.ac.uk/random/

(available 24 hours a day)

14. Blinding

Assignment to either active or placebo arm will be blinded to both the participant and investigators/assessor (double-blind). A code-break list will be kept in pharmacy; this list should be accessed only in an emergency (preferably with authorisation from the Chief Investigator or Medical Monitor) and the Chief Investigator immediately informed. If the code is broken, details including the participant number, the person who broke the code, why and when the code was broken shall be recorded and maintained in the site file. Code breaks will not be routinely opened for participants who complete study treatment.

At the final visit, the integrity of the blind will be assessed by asking both the participants and their treatment assessor: "Do you think you were receiving Rituximab or the dummy solution? Why do you think this?" The treatment assessor will be asked to record their answer on a separate CRF, and prior to asking the participant to avoid bias.

15. Study Data

Patients will be randomised to receive two infused doses of Rituximab (1000 mg IV) or placebo (0.9% Sodium Chloride 250mls) at visit 2 (day 1) and visit 4 (day 15). In line with recommendations, a conditioning regimen consisting of Paracetamol 1g PO, Chlorphenamine 4mg PO, and Methylprednisolone 100mg IV will be given 30 minutes before each infusion of Rituximab/placebo. Intervention will be given in the setting of a dedicated immunotherapy clinical trials unit.

The proposed clinical trial is single centred, and will be performed in the Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH). Recruitment will principally be from the large clinical cohort under follow-up at this centre (>500, the largest clinical PBC service in the UK). If needed, additional patients will be signposted via the Northumberland Tyne and Wear and County Durham and Tees Valley CLRNs (consisting of an additional 10+ clinical centres managing PBC patients) and participation identification centres established via the CLRN Hepatology Speciality Groups and the Autoimmune Study Group. In addition if required CLRNs across the North of England will be approached for additional patients. The applicants have an established track record of success in recruiting PBC participants into trials and other clinical studies in PBC.

15.1 Schedule of events

VISIT 0 (Screening): After unrestricted opportunity to discuss the study, informed consent will be taken. Following consent participants will have a full clinical history taken which will include a detailed record of concomitant medication and will undergo a physical examination (including vital signs, height and weight). Screening for chronic infection in the form of HCV and HBV serology (Hepatitis C antibody, Hepatitis B surface antigen and core antibody) will be undertaken.

VISIT 1 (Baseline and randomisation): Any changes in concomitant medication will be noted. A pregnancy test will be performed on female participants. Baseline blood tests will be performed full blood count, U&Es, liver function tests (including AST and GGT), random lipid profile (including total cholesterol, HDL, triglycerides), autoantibodies, immunoglobulins, coagulation studies and CRP. Blood will be taken for the baseline assessment of serum, RNA and white cells. Patient questionnaires (PBC-40, PROMIS HAQ, COGFAIL, ESS, OGS and HADS) will be completed. Participants will be issued with a fatigue diary. They will be asked to complete it for a period of one week at the beginning of each month for each visit at baseline, 1, 3, 6, 9 and 12 months.

The participant will be randomised into either the control or Rituximab treatment arm. Participants will undergo the pre-treatment MRI muscle assessment and anaerobic threshold and will commence a 7 day physical activity assessment using activity monitors.

VISIT 2 (1st Infusion): Following clinical re-assessment (including physical examination and vital signs and recording of any changes in concomitant medication), repeat blood draw for LFT, FBC, U&Es and CRP will be performed. Participants will undergo the first trial infusion as outlined in the infusion protocol. Participants will be monitored during and after the infusion and adverse events noted.

VISIT 3 (Safety visit): Following the first infusion, adverse events will be noted and explored as appropriate and physical examination will be performed and vital signs recorded. Changes in concomitant medication will be noted. Repeat blood tests will be performed (FBC, LFT, U&Es, random lipid profile and CRP).

VISIT 4 (2nd Infusion): Following clinical re-assessment (including physical examination and vital signs and recording of any changes in concomitant medication and recording of any adverse events following treatment 1), repeat blood draw for LFT, FBC, U&Es and CRP will be performed. Participants will undergo the second trial infusion as outlined in the infusion protocol. Participants will be monitored during and after the infusion and adverse events noted.

VISITS 5-15 (Monitoring): Patients will be contacted with telephone calls by a Research nurse. Adverse events will be noted and explored as appropriate. Changes in concomitant medication will be noted.

VISIT 16 (Mechanistic Assessment): Adverse events will be noted and explored as appropriate. Changes in concomitant medication will be noted. Participants will undergo the post-treatment MRI muscle assessment and anaerobic threshold, physical examination, vital signs and repeat blood tests will be performed (FBC, LFT, U&Es, random lipid profile, serum, RNA and white cells autoantibodies, immunoglobulins, coagulation studies and CRP) and physical activity assessment as performed on visit 1 will be repeated (monitor to be returned by post or taxi at the end of the assessment period) and repeat patient questionnaires (PBC-40, PROMIS HAQ, COGFAIL, ESS, OGS and HADS). Participants will be reminded to complete the fatigue diary for one week at the beginning of the month at this 3 month visit.

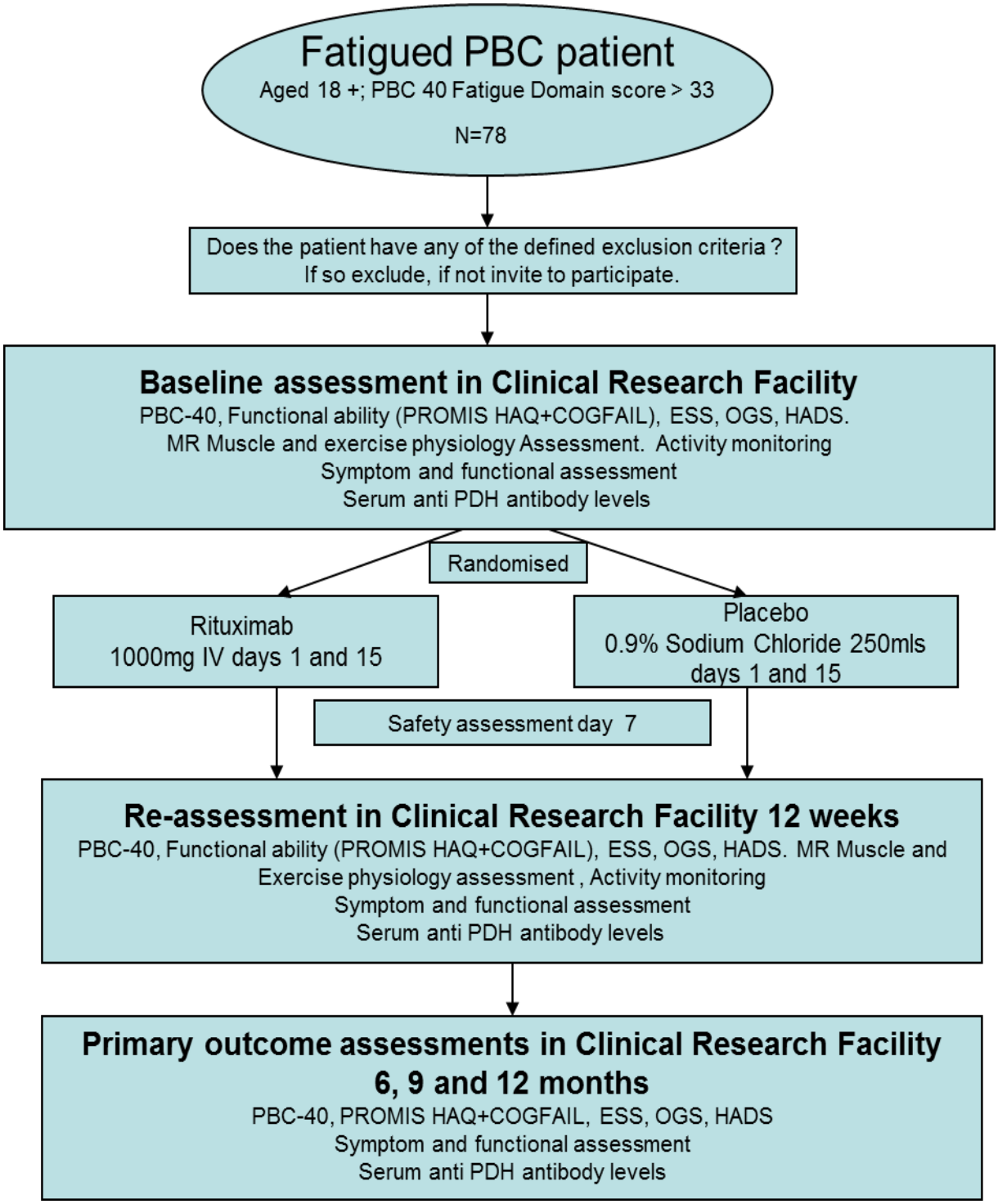
VISITS 17, 18 and 19 (6, 9 and 12 Months (Primary Outcome Assessment)): Adverse events will be noted and explored as appropriate. Changes in concomitant medication will be noted. Physical examination, vital signs and repeat blood tests will be performed (FBC, LFT, U&Es, random lipid profile and CRP) and repeat patient questionnaires (PBC-40, PROMIS HAQ, COGFAIL, ESS, OGS and HADS). Blood will be taken for the assessment of serum, RNA and white cells. Participants will be reminded to complete the fatigue diary for one week at the beginning of the month at the 6, 9 and 12 month visits. At visit 19 (final visit) participants will return their completed fatigue diary.

A complete breakdown of patient visits is outlined in the table of events below:

	Visit 0 Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visits 5-15	Visit 16	Visit 17	Visit 18	Visit 19 Final
	-2 Weeks	Baseline and Randomisation	Day 1 1st infusion	Day 7 Safety Visit	Day 15 2nd infusion	Treatment +1-11 weeks	Treatment +12 weeks	Treatment + 6 months	Treatment + 9 months	Treatment + 12 months
Physical examination[1]	X		X	X	X	TELEPHONE REVIEW/ CONCOMITANT MEDICATIONS/ THERAPIES CHECK AND AE REVIEW	X	X	X	X
Obtain informed consent	X									
Pregnancy test		X								
Hep B/C[5]	X									
PBC- 40		X					X	X	X	X
PROMIS HAQ questionnaire		X					X	X	X	X
COGFAIL questionnaire		X					X	X	X	X
HADS questionnaire		X					X	X	X	X
Issued Fatigue diary[2]		X								
Return Fatigue diary										X
ESS/OGS questionnaires		X					X	X	X	X
FBC, LFT, U&Es and CRP[3]		X	X	X	X		X	X	X	X
Random lipid profile[4]		X		X			X	X	X	X
Autoantibodies &		X					X			
Coagulation studies		X					X			
Adverse events			X	X	X		X	X	X	X
Concomitant medication	X	X	X	X	X		X	X	X	X
Activity monitors		X					X			
Blood for serum, RNA and white		X					X	X	X	X
Muscle MRI		X					X			
Anaerobic threshold		X					X			
Randomisation		X								
Rituximab / placebo infusion			X		X					

1.Physical examination includes vital signs (height, weight, blood pressure, heart rate, temperature and respiratory rate)
2. Patients are issued with Fatigue diary at Baseline and are asked to complete it for a one week period at the beginning of each month for each visit at baseline, 1, 3, 6, 9 and 12 months. They return it at visit 19.
3. LFT includes AST and GGT
4. Random lipid profile includes total cholesterol, HDL and triglycerides
5. Hepatitis B serology test including HBsAg (Hepatitis B surface antigen) and HBc (Hepatitis B core antibody)

Table 1 - Schedule of Events



15.2 Data collection

Each patient will undergo a screening period (following written consent) of up to 14 days prior to entry into study. Patients who are eligible to enter into the study will be randomised between the two treatment groups and will receive two infusions of study medication (days 1 and 15). If significant adverse reactions occur, an overnight stay may be required. Participants will be assessed for treatment related-toxicity in the week following each infusion. Follow-up telephone assessments will be performed weekly for 12 weeks following the second infusion. The study is expected to be open for enrolment for 24 months. Assessment of primary endpoint and mechanistic and safety secondary endpoints will be made at 12 weeks after the second infusion. Sustainability of the response will be assessed by secondary clinical follow-up and PBC-40 assessment undertaken 3 monthly until 12 months have elapsed from treatment.

To preserve confidentiality, all patients will be allocated a unique study identification number, which will be used on all data collection forms and questionnaires; names and addresses will not appear on completed questionnaires or case report forms. Only a limited number of members of the research team will be able to link this identification number to identifiable details (name and address) which will be held on a password-protected database. All study documentation will be held in secure offices and the research team will operate to a signed code of confidentiality. Data collected on paper Case Report Forms (CRFs) will be entered by the research nurse from the Newcastle Clinical Research Facility (NCRF). Transmission of identifiable data between Newcastle Clinical Trials Unit (NCTU) and the Newcastle upon Tyne Hospitals NHS Foundation Trust (the study Sponsor) will be by a study team member. MACRO, a clinical data management software package will be used for data entry and processing, allowing a full audit trail of any alterations made to the data post entry. Original questionnaires, CRFs and consent forms will be securely archived at the Newcastle upon Tyne Hospitals NHS Foundation Trust archive facility for fifteen years following publication of the last paper or report from the study.

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site.

The quality and retention of study data will be the responsibility of the Chief Investigator. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

16. Statistical considerations

16.1 Statistical analysis

PBC-40 fatigue domain score at 12 week assessment as outlined in section 9.

Safety: Assessed in terms of numbers of adverse events and adverse reactions in the study groups.

Activity: Habitual physical activity will be measured objectively using two activity monitors: 1) a validated multi-sensor array (SenseWear Pro$_3$**,** Bodymedia Inc, PA, USA) worn continuously over 7 days immediately prior to the first infusion and during week 12 of the follow-up period. The multi-sensor array measures 4 key metrics; skin temperature, galvanic skin response, heat flux and motion via a 3-axis accelerometer. The sensors combined with algorithms, calculate the average daily energy expenditure relative to baseline metabolism (metabolic equivalent: MET per day [1MET=resting metabolic rate]), total energy expenditure (calories per day), active energy expenditure (total calories expended over 3METS per day), physical activity duration (min over 3METS per day) and average daily number of steps walked. Patterns of sedentary behaviour will be assessed by power law analyses of the lengths of sedentary bouts fitted from raw sedentary data. Probabilities of bout lengths will be plotted against the fraction of total sedentary time. Activity patterns will also assessed by assessing transitions from active to inactive period, termed "zero-crossing rate" and normalized by the length of the recording. Outcome measure for study evaluation will be mean number of steps/24 hours before and at follow-up in the two study groups. 2) The GENEActiv (ActivInsights, Ltd) is a waterproof, lightweight (16 grams) triaxial accelerometer. This wrist worn accelerometer can be worn continuously to collect 24 hour monitoring. Raw accelerations are collected at a range of +/- 8g with the recording frequencies ranging from 10-100Hz. Data will be collected for this trial at a frequency of 40Hz and worn continuously for 7 days.

Other Clinical Symptoms and Functional capability*:* Other symptom severity will be assessed in terms of numerical change for the relevant domain of the PBC-40 (Itch, Cognitive Symptoms, social and Emotional Symptoms). Functional status will be assessed using the PROMIS HAQ to assess function[10]. The PROMIS HAQ measures the functional and physical ability of the participants (covering, dressing, arising, eating, walking, hygiene, reach, grip and activity). The score is on a 0-100 scale with higher scores indicating worse functional ability. Depression will be assessed by HADS score. Improvement in daytime somnolence will be assessed using ESS. Vasomotor autonomic symptoms will be assessed using OGS.

Diaries: Participant held diaries will be used as a means of capturing clinical interventions and gather qualitative information as to symptoms and functional ability. We have successfully used diaries that include both structured (quantitative) and unstructured (qualitative) methods of data collection. The diaries measure fatigue using a scale of 1 to 6, 1 – no fatigue and 6 – extreme fatigue. Participants will be asked to complete the diaries six times during the study. They will complete the diaries for a period of a week at the beginning of each month at visits: baseline, 1, 3, 6, 9 and 12 months. They will return the diaries at the final visit (19).

Time course of clinical benefit: Further change in PBC-40 between 12 weeks and 12 months

B-Cell depletion: Quantification and phenotyping of total B-cell populations and B-cell subsets will be by a FACS-based approach using well-described approaches utilizing markers other than CD20[11]. Outcome measure will be change in individual parameters with therapy. Total and activated B-cells in peripheral blood will be evaluated using a direct immune-fluoresence reagent (Fast Immune CD19/CD69/CD45, BD Biosciences). CD19 is present on all B-cell subsets other than plasma cells, CD69 is an early lymphocyte activation marker and CD45 is a general leucocyte marker. Briefly, 20µl of reagent is added to 50µl whole blood and incubated in the dark for 15 mins. 450µl of FACS™ lysing solution is added and incubated in the dark for 20mins. The samples will then be analysed using a FACSCalibur™ flow cytometer. Additionally, memory B cells (CD19+/CD27+/CD38-) and plasma cells (CD19-/CD27++/CD38+) will be quantified following staining with appropriate combinations of labelled antibodies (BD) and subsequent flow cytometry.

The population of B-cells carrying an antigen specific (anti-PDH) B-cell receptor (BCR) will be visualised and enumerated using an in-house high avidity antigenic, R-phycoerythrin (RPE labelled) tetramer by fluorescence microscopy and flow cytometry. We will initially isolate B-cells using CD19 Microbeads (Miltenyi Biotech) and then identify PDH-specific cells using tetramer. To generate the immuno-reactive antigen to be incorporated in the tetramers we will use Biotin AviTag™ technology (Avidity, Colorado, USA) to genetically engineer a construct in the pAN series of vectors to encode PDH-E2 inner lipoyl domain (11kDa) fused to an N-terminal Biotin AviTag sequence. This is a unique peptide, only 15 residues long, that is recognised by biotin ligase which, in the presence of ATP, specifically attaches biotin to the lysine residue in this sequence. Efficient biotinylation will be achieved by expressing the PDH-E2 inner lipoyl domain fusion protein in the IPTG inducible AVB101 *E.Coli* B strain (Avidity). AVB101 contains the pACYC184 ColE1 compatible plasmid that over-expresses the Biotin Ligase which in the presence of free biotin ensures complete biotinylation if the AviTag sequence. Over-expressed biotinylated PDH-E2 inner lipoyl domain will be affinity purified from clarified *E.coli.* extracts using SoftLink Soft Release Avidin Resin (Promega). This monomeric avidin allows reversible binding of biotinylated proteins under mild elution conditions (free biotin). The purified N-terminally biotinylated PDH-E2 inner lipoyl domain will then be complexed with R-phycoerythrin (RPE) labelled neutravidin to form stable tetramers. Inhibiting (competing) tetramers using unlabelled neutravidin will also be generated to be used in control studies. Tetramer will be incorporated in FACS studies to determine degree of depletion specifically of PDH-reactive B-cells with Rituximab therapy.

Anti-PDH Antibody Reactivity: PBC is characterised by autoantibody directed at PDH which is highly effective at inhibiting PDH function *in vitro*. Autoantibody of all isotypes can be quantified using ELISA, with the IgG3 fraction typically predominating. Anti-PDH can also be quantified using a PDH-inhibition-based functional assay; an assay of relevance given the hypothesis being tested in the proposed study. Pilot studies of Rituximab in PBC have demonstrated sustained reduction in anti-PDH antibody of all isotypes. Anti-PDH antibody total and individual isotype levels and antibody functional inhibitory capacity will be studied on day 0 and at the primary end point (12 weeks after therapy). Antibody levels will also be correlated with long term fatigue status during the secondary follow-up period to 12 months. Anti-PDH levels and isotype patterns will be assessed using a well established ELISA developed within our research group[12]. A variety of highly purified native autoantigens (bovine and human PDH) and recombinant (full-length E2 component or the major autoantigenic E2 inner

lipoyl domain epitope) will be employed as coating antigens on Immulon 4HBX 96 well microtitre plates (5µg/ml). Detection of bound anti-PDH antibodies will be detected using goat anti-human IgG (including individual IgG1-4 isotypes), IgM and IgA peroxidase conjugated antibody (Sigma). Bound peroxidase activity will be visualised using o-phenylenediamine and measured at 492nm[32]. Anti-PDH inhibitory activity will be assessed using an established assay[13]. In this assay, PDH activity will be measured at 30°C by monitoring the production of nicotinamide adenine dinucleotide (NADH) at 340 nm. The reaction is initiated by the addition of 2mM pyruvate, to a mixture containing diluted purified bovine PDH, 50mM KPO_4, 0.2mM TPP, 1mM $MgCl_2$, 2.5 mM NAD, 0.13mM coenzyme A, 2.6mM cysteine hydrochloride, in a final volume of 1ml at pH7.4. One unit of enzyme activity catalyses the production of 1µmol of NADH per minute. Before initiating the reaction, serum samples (5µl) are incubated for 30 minutes at 30°C with the PDH containing mixture. Inhibitory capacity of sera is assessed as a percentage of reactivity observed when pre-incubated with phosphate-buffered saline. The specific anti-lipoic acid component of the anti-PDH antibody response will be quantified using the subtractive approach previously described by Bruggraber et al[14]. In the analysis phase impact of Rituximab on fatigue in PBC will be correlated with changes in individual autoantibody isotype responses and with PDH-inhibitory capacity of serum.

Muscle Acidosis*:* Magnetic resonance data will be acquired prior to first infusion and after 12 weeks follow-up using a 3T Intera Achieva scanner (Philips, Best, NL) with a 14cm diameter ^{31}P surface coil for transmission/reception of signal and the in-built body coil for anatomical imaging. The protocol used for acquisition and analysis has been described fully elsewhere but briefly involved controlled plantar flexion using a purpose-built exercise apparatus developed for operation within the MRI scanner [15]. Participants will perform 2 x 180s bouts of plantar flexion contractions at 25% and then 35% of MVC, with each bout preceded by 60s of rest and followed by 390s of recovery. Phosphorous spectra will be collected at 10s intervals, as previously described[15]. Quantification of spectra will be undertaken using the jMRUI software with metabolite concentrations and metabolic calculations performed as described previously. In particular we will evaluate the minimum pH seen in the exercise and recovery period, the time required post-exercise for pH to return to within 0.01 units of baseline levels (calculated as the sum for each individual for the three bouts to form a total pH recovery time) and the mean "area under the curve" for pH for the 3 exercise episodes which reflects total acid exposure.

Anaerobic Threshold: Participants will cycle on a stationary ergometer (Corival, Lode, Nederland) at between 60-90rpm. The test will be terminated voluntarily by the participant or when they were unable to maintain a pedal frequency of 60 revolutions per minute (RMP). Expired air will be collected at rest and during exercise using a breathing mask and analysed online using a gas analysis system (MetaLyzer II, CORTEX, Germany) and heart rate (Polar Electro, Polar, Finland). Peak cardiovascular fitness will be calculated in metabolic equivalents (one MET is equivalent to the oxygen consumption whilst laying quietly or approximately 3.5 ml/kg/min oxygen consumption). Anaerobic threshold will be assessed using the computerised v-slope method and values compared for before and after therapy as the outcome measure.

Liver Disease Activity: Although not powered to demonstrate biologically significant effects on severity of underlying liver disease the study will provide important pointers to any effect which would inform the design of future studies. Change in serum biochemical end-points has been accepted by

The Food and Drug Association (FDA)as an appropriate end-point for clinical trials in PBC[8]. The outcome measure which we will use will be reduction in serum alkaline phosphatase level and attainment of the previously identified positive outcome measure of drop in baseline alkaline phosphatase of >40% or normalisation (the "Barcelona Criteria"[16]).

16.2 Sample size calculation

A total sample size of 58 participants (29 per arm) will be recruited and randomised; this includes an assumption of 10% attrition at 12-week follow-up (based on experience in clinical trials in PBC). The primary outcome is the PBC-40 fatigue domain score (range 11-55) after 12 weeks of intervention. The standard deviation of fatigue scores is 8 units (based on the PBC-40 derivation studies utilising >1000 patients[6]), with a correlation of 0.6 between baseline and follow-up time points based on previous linear studies. The study is powered to detect a mean change in PBC-40 fatigue domain score of 5 units (equating to an average of 0.5 point change per question; a difference in PBC-40 score demonstrated in our population-based studies to be associated with significantly higher levels of social function and which was therefore deemed to be clinically significant for the purposes of the study design) with a power of 80% and a 5% significance level. This equates to 26 participants in each group providing data on the primary outcome (PBC-40 fatigue score at 12 weeks): incorporating an assumption of a 10% attrition gives a total of 58. The number of participants lost to follow-up, or withdrawing consent prior to initial treatment is expected to be minimal. The Data Monitoring and Ethic Committee (DMEC) may advise recruitment of additional participants if numbers withdrawing or lost to follow-up are higher than anticipated.

16.3 Analysis of outcome measures

Analysis will be on the basis of intention to treat.

Primary: Differences between intervention and control groups at 12 weeks on PBC-40 fatigue domain scores will be analysed by analysis of covariance (ANCOVA) using baseline scores as covariates. The time course of the comparison between intervention and control groups over the 12 month follow-up period will be assessed using repeated measures analysis of variance.

Secondary: Secondary outcomes, covering comparison of other clinical symptom and functional capability scales at 12 weeks will also be analysed by ANCOVA using baseline values as covariates. The time course of the comparison between intervention and control groups over the 12 month follow-up period will be assessed using repeated measures analysis of variance.

The analysis of the mechanistic variables will be more descriptive in nature, and will involve comparison of means or proportions between intervention groups, as appropriate, and the use of correlation coefficients to explore the relationship between physiological/immunological measurements and fatigue.

16.4 Final analysis

There are no planned interim analyses for efficacy. However if the DMEC requires interim analysis for safety then this will be performed. Final analyses will be carried out when all participants have been followed up.

17. Compliance and withdrawal

17.1 Assessment of compliance

Where feasible, study visits will coincide with routine clinical follow-up, to enhance the likelihood of good compliance. Visit windows of +/-3 days should ensure visit attendance; non-attendance for study visits will prompt follow-up by telephone.

17.2 Withdrawal of participants

Study drug must be discontinued if:

- the participant develops elevated serum Alanine Transaminase (ALT)/Aspartate Transaminase (AST) 4 times above normal limits for each local laboratory
- the participant decides she/he no longer wishes to continue
- cessation of study drug is recommended by the investigator

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, adverse events, serious adverse events, suspected unexpected serious adverse reactions, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from study medication will be asked to confirm whether they are still willing to provide the following:

- study specific data at follow-up visits 5 to 19
- end of study data as per visit 19, at the point of withdrawal
- questionnaire data collected as per routine clinical practice at annual follow-up visits
- if participants agree to any of the above, they will be asked to complete a confirmation of withdrawal form to document their decision.

Participants who withdraw from study after receiving the second infusion will not be replaced.

18. Data monitoring, quality control and quality assurance

18.1 Discontinuation rules

The study may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring and Ethics Committee and/or Trial Steering Committee, Sponsor, regulatory authority or Research Ethics Committee concerned.

Following six months of recruitment, initial rates of recruitment will be used to project total recruitment to ensure sufficient participants to power the study. The Trial Steering Committee will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

18.2 Monitoring, quality control and quality assurance

The study will be managed through the Newcastle Clinical Trials Unit (NCTU). The Trial Management Group (TMG) will include: the Chief Investigator, Senior Trial Manager, Trial Manager, Assistant Trial Manager, Data Manager and other members of the trial team when applicable.

NCTU will provide day-to-day support for the site and provide training through Investigator meetings, site initiation visit and routine monitoring visits.

The Principal Investigator will be responsible for the day-to-day study conduct at site.

Quality control will be maintained through adherence to NCTU SOPs, NUTH SOPs, National Medical Research Council (NMRC) SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations.

Data Monitoring and Ethics Committee (DMEC)

An independent data monitoring and ethics committee (DMEC) has been appointed. It will consist of: two physicians not connected to the study and one independent statistician and will be convened to undertake independent review. The purpose of this committee will be to monitor efficacy and safety endpoints. Only the DMEC will have access to unblinded study data. The committee will meet at least three times, at the start, middle and completion of the study.

Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established to provide overall supervision of the study. The TSC will consist of an independent chair, two independent clinicians, independent consumer representative, the Chief Investigator, Co-investigator, Senior Trial Manager, Trial Manager and trial statistician. Representatives of the Trial Sponsor and Funder should be invited to all TSC meetings. The committee will meet every 3 months during recruitment, and annually thereafter for the duration of the study.

The side effect profile of Rituximab is well established and major safety data is not anticipated. Following the initial pre-study meeting, the TSC will meet annually.

Study Monitoring

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by the Trial Manager. The main areas of focus will include consent, serious adverse events, essential documents in study site files and drug accountability and management.

Site monitoring will include:

- All original consent forms will be reviewed as part of the study site file. The presence of a copy in the patient hospital notes will be confirmed for 20% of participants
- All original consent forms will be compared against the study participant identification list
- All reported serious adverse events will be verified against treatment notes/medical records (source data verification)
- The presence of essential documents in the investigator site file and study files will be checked
- Source data verification of primary endpoint data and eligibility data for 20% of participants entered in the study
- Drug accountability and management will be checked

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission
- All documentation essential for study initiation will be reviewed prior to site authorisation

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by the Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit study-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents.

19. Pharmacovigilance

19.1 Definitions

Adverse event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the IMP qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality:

The local investigator responsible for the care of the participant will be asked to assign causality, in accordance with the study protocol. An example of how causality may be defined is described in the table below. All adverse events judged by either the Investigator or Sponsor as having a reasonable suspected causal relationship (i.e. definitely, probably or possibly related) to the IMP(s) are considered to be adverse reactions. If any doubt about the causality exists, the local investigator must inform the Sponsor (or authorised delegate) as per study protocol. Where a second assessment of an event takes place (e.g. by Sponsor), the causality assessment by the local Investigator cannot be downgraded. In the case of discrepant views on causality, all parties will discuss the case. In the event that no agreement is made, both views will be documented. The MHRA, main REC and other bodies (as relevant) will be informed of both points of view if the event is reportable.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication/procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication/procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

* *All adverse events judged as having a reasonable suspected causal relationship to the IMP(s) (i.e.* ***definitely, probably or possibly*** *related) are considered to be* ***adverse reactions****.*

Serious Adverse Event / Reaction (SAE/SAR)

An adverse event or adverse reaction that:

- results in death
- is life-threatening
- requires hospitalisation, or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
  or
- is a congenital anomaly or birth defect.

The term life-threatening refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Unexpected Adverse Reaction (UAR)

Any adverse reaction, the nature and severity of which is not consistent with the reference safety information about the medicinal product in question, set out:

a) In the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SmPC) for that product.

b) In the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.

Suspected Serious Adverse Reaction (SSAR)

Any adverse **reaction** that is classed as **serious** as defined above.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse **reaction** that is classed as **serious** and **unexpected** as defined above. An adverse reaction is 'unexpected' if its nature or severity is not consistent with the applicable product information (refer to Appendix 1).

Severity of Adverse Events

The term "severe" is often used to describe the intensity (severity) of a specific event. For example, a three-point scale of intensity may be defined in the study protocol to grade all AEs:

- **Mild:** Discomfort is noticed, but there is no disruption of normal daily activities
- **Moderate:** Discomfort is sufficient to reduce or affect normal daily activities
- **Severe:** Discomfort is incapacitating, with inability to work or to perform normal daily activities

Severity is **not** the same as "serious", which is based on patient/event outcome or action criteria. An AE may be severe but not serious.

Expected adverse reactions:

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. For a full list of expected undesirable effects of Rituximab, please refer to the Summary of Product Characteristics for Rituximab (Appendix 1).

Protocol specifications

For purposes of this protocol:

- All non-serious adverse reactions will be recorded at visits 2 – 19
- Any serious adverse events will be recorded throughout the duration of the trial until 12 months after trial therapy is stopped
- Serious adverse events exclude any pre-planned hospitalisations (e.g. elective surgery) not associated with clinical deterioration
- Serious adverse events exclude routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Serious adverse events exclude fatigue [primary outcome measure, already documented and monitored within study]

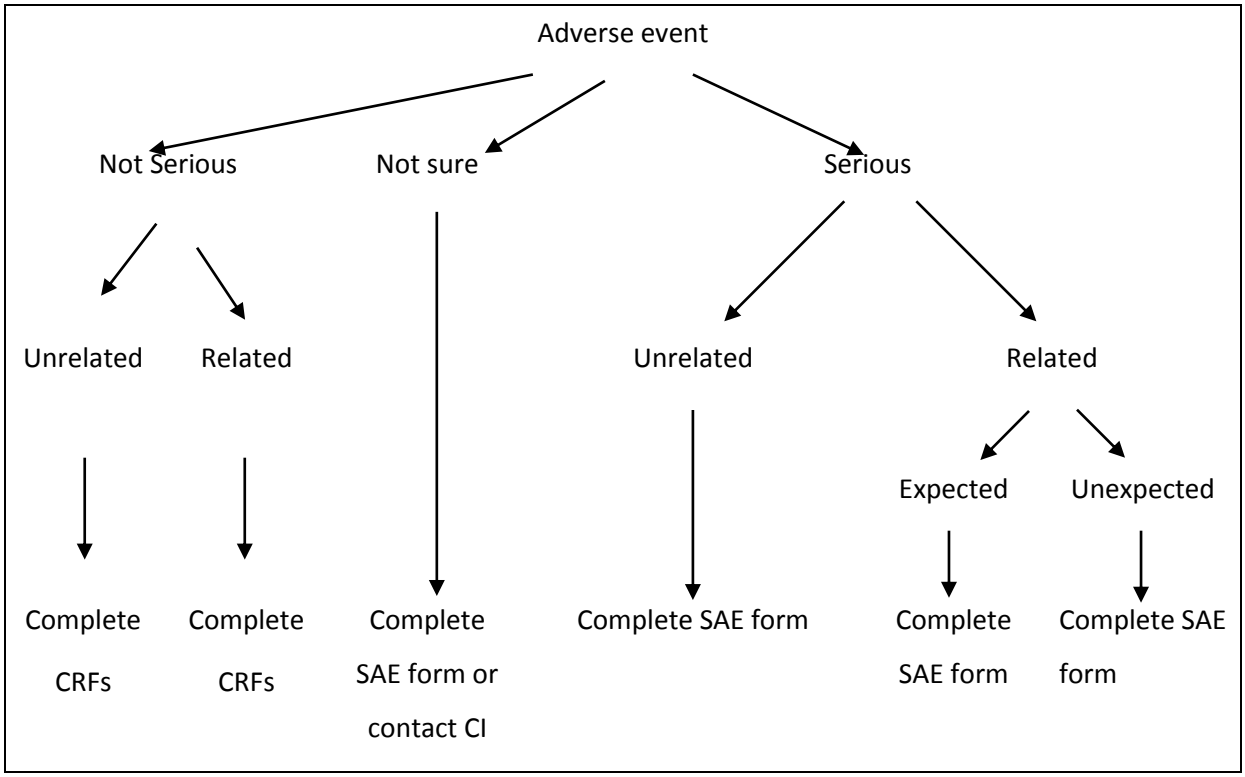
Adverse Reactions During Treatment Administration

During the infusion patients will be monitored clinically for the onset of clinical features of infusion-related reactions (IRR, the commonest adverse events in Rituximab usage). Patients who develop evidence of severe IRR, especially severe dyspnoea, bronchospasm or hypoxia, will have the infusion interrupted immediately. The infusion will not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half of the previous rate. If the same severe adverse reactions occur for a second time the treatment will be stopped. Mild or moderate IRR will be addressed by halving of the rate of infusion. The infusion rate may be increased again upon improvement of symptoms. Paracetamol and/or NSAIDS can be prescribed for the symptomatic management of IRRs.

Recording and Reporting Serious Adverse Events or Reactions:

All adverse events should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator or the named contact within the management team within the NCTU (Dr Alison Steel, Trial Manager) in the first instance. A flowchart (figure 1) is given below to aid in the reporting procedures.

Figure 1



Adverse Event (including Adverse Reaction):
All non-serious adverse events / reactions during drug treatment will be reported on the study CRF and sent to the NCTU management team within 2 weeks of the form being due. Severity of AEs will be graded on a five-point scale (mild, moderate, severe, life threatening, causing death). Relation of the AE to the treatment should be assessed by the investigator at site. The individual investigator at each site will be responsible for managing all adverse events / reactions according to local protocols.

Serious Adverse Event / Reaction (SAE/SAR, including SUSARs):
All SAEs, SARs and SUSARs during drug treatment shall be reported to the Chief Investigator within 24 hours of the site learning of its occurrence. The initial report can be made by filling the SAE form and sending to the SAE reporting system by Fax via the SOHO66 system on 0191 5800432 or telephoning 0191 2087623 (Mon to Fri 09.00 – 17.00). In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available. Relationship of the SAE to the treatment should be assessed by the Investigator at site, as should the expected or unexpected nature of any serious adverse reactions.

The MHRA and main REC will be notified by the Chief Investigator or trials management team (on behalf of the Sponsor) of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. SUSARS will be reported using a CIOMS 1 form, specifying the EudraCT number, CTA number, protocol number and study name, and the data elements listed in Annex 3 of *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006*.

All investigators will be informed of all SUSARs occurring throughout the study on a case-by-case basis.

The Chief Investigator will ensure the Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SUSARs in accordance with local Trust policy.

Contact details for reporting SAEs

Please send SAE form(s) to Newcastle Clinical Trials Unit FAO RITPBC Trial Manager
Fax: 01915800432
Telephone: 0191 2087623 (Mon to Fri 09.00 – 17.00)

The initial report can be made by secure fax which will also generate an email copy to the Chief Investigator, Senior Trial Manager and Trial Manager. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up, on the appropriate SAE follow-up form. As indicated above, relationship of the SAE to the treatment (causality) should be assessed by the investigator at site, as should the expected or unexpected nature (by reference to the SmPC for Rituximab) of any serious adverse reactions.

19.2 Pregnancy and contraception

If a female participant does become pregnant while participating in the study, study drug(s) will be discontinued immediately and the patient withdrawn from the study. Details of the pregnancy should be reported to the Chief Investigator within 24 hours of learning of its occurrence. The pregnancy must be followed up following local protocols in place to determine outcome. Due to the long retention time of Rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following Rituximab therapy (in line with the SmPC for Rituximab).

19.3 Abnormal Magnetic Resonance (MR) findings

Research MR scans undertaken at the Newcastle Magnetic Resonance Centre (NMRC) are for research, not clinical purposes. As such they will not be routinely examined or reported by a clinical radiologist. The Chief Investigator and other study personnel will ensure that subjects undergoing such scans are made aware of this in advance and this is outlined in the Participant Information Sheet. However, it is possible that, in the course of performing the scans, an NMRC radiographer may identify a previously unsuspected structural abnormality. In this event, the scan images will be referred by the radiographer to a qualified consultant radiologist from the Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) for a clinical radiological opinion. There is an existing protocol between the NMRC and the NUTH Trust whereby consultant radiologists from NUTH receive such requests from NMRC staff on a monthly rotation. This rota is available at all times at the NMRC for radiographers to refer to. In the event that an NMRC radiographer decides to refer a scan in this manner, they will inform the CI (Prof Jones) and the Co-Investigator responsible for the NMRC work (Prof Blamire) within 24 hours. The CI will then discuss the case with the relevant radiologist as soon as the report is available. The CI will then arrange to refer the patient to other specialists as appropriate. The decision as to what further action is needed, including how to communicate such findings to the subject and their GP, will be the responsibility of the study CI on a case-by-case basis.

20. Ethics and regulatory issues

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Favourable ethical opinion and Clinical Trial Authorisation from the relevant Competent Authority will be sought prior to commencement of the study. Local approval will be sought before recruitment may commence at the site. The Study Coordination Centre will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Information sheets will be provided to all eligible subjects and written informed consent obtained prior to any study procedures. For subjects who cannot consent for themselves, an appropriate independent witness will provide written consent.

21. Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study identification code only. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

All laboratory samples will be labelled with a unique study identification number and patients' date of birth only (linked in anonymised form).

22. Insurance and finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the study for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation NHS Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantative contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with Newcastle University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

MRC and NIHR Efficacy and Mechanism Evaluation Programme, and a DoH subvention grant are funding the study.

23. Study report / publications

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

It is planned to publish this study in peer review journals and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any study report.

Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results.

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25. Appendices

Appendix 1. Rituximab Summary of Product Characteristics

Appendix 2. Latest version of the Declaration of Helsinki (to document and outline the ethical principles for medical research involving human subjects)

Appendix 3. Questionnaires / Measurement tools (PBC-40, PROMIS HAQ, COGFAIL, ESS, OGS, HADS)

Appendix 4. Fatigue Diary

Appendix 5. Rituximab infusion guidelines

Appendix 6. Trial Steering Committee terms of reference

Appendix 7. Data Monitoring Ethics Committee terms of reference

Appendix 1. Rituximab Summary of Product Characteristics

Mabthera 100mg and 500mg concentrate for solution for infusion

Summary of Product Characteristics Updated 06-Jun-2014 | Roche Products Limited

1. Name of the medicinal product

MabThera 100 mg concentrate for solution for infusion
MabThera 500 mg concentrate for solution for infusion

2. Qualitative and quantitative composition

Each mL contains 10 mg of rituximab.
10mL vial: Each vial contains 100 mg of rituximab.
50mL vial: Each vial contains 500 mg of rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Concentrate for solution for infusion.
Clear, colourless liquid.

4. Clinical particulars

4.1 Therapeutic indications

MabThera is indicated in adults for the following indications:
Non-Hodgkin's lymphoma (NHL)
MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)
MabThera in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are

available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy.

See section 5.1 for further information.

Rheumatoid arthritis
MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

MabThera has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and microscopic polyangiitis
MabThera, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

4.2 Posology and method of administration

MabThera should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available (see section 4.4).

Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera.

In patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy.

In patients with rheumatoid arthritis, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to MabThera infusions to decrease the incidence and severity of infusion related reactions (IRRs).

In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, methylprednisolone given intravenously for 1 to 3 days at a dose of 1000 mg per day is recommended prior to the first infusion of MabThera (the last dose of methylprednisolone may be given on the same day as the first infusion of MabThera). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after MabThera treatment.

Posology
It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient, as prescribed.

Non-Hodgkin's lymphoma
Follicular non-Hodgkin's lymphoma
Combination therapy

The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles.

MabThera should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.

Maintenance therapy
• Previously untreated follicular lymphoma
The recommended dose of MabThera used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

• Relapsed/refractory follicular lymphoma
The recommended dose of MabThera used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.
Monotherapy

• Relapsed/refractory follicular lymphoma
The recommended dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma
MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

<u>Dose adjustments during treatment</u>
No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

<u>Chronic lymphocytic leukaemia</u>
Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion.

Rheumatoid arthritis
Patients treated with MabThera must be given the patient alert card with each infusion.
A course of MabThera consists of two 1000 mg intravenous infusions. The recommended dosage of MabThera is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.

The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns.

Available data suggest that clinical response is usually achieved within 16 - 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Granulomatosis with polyangiitis and microscopic polyangiitis
Patients treated with MabThera must be given the patient alert card with each infusion.
The recommended dosage of MabThera for induction of remission therapy of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with granulomatosis with polyangiitis or microscopic polyangiitis during and following MabThera treatment, as appropriate.

Special populations
Paediatric population
The safety and efficacy of MabThera in children below 18 years has not been established. No data are available.

Elderly
No dose adjustment is required in elderly patients (aged >65 years).

Method of administration
The prepared MabThera solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.

Patients should be closely monitored for the onset of cytokine release syndrome (see section 4.4). Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.

Mild or moderate infusion-related reactions (IRR) (section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

First infusion
The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Subsequent infusions
All indications
Subsequent doses of MabThera can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.
Rheumatoid arthritis only
Alternative subsequent, faster, infusion schedule

If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1000 mg MabThera administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/mL in a 250 mL volume). Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.

Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

4.3 Contraindications

Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients listed in section 6.1.
Active, severe infections (see section 4.4).
Patients in a severely immunocompromised state.

Contraindications for use in rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis
Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients listed in section 6.1.
Active, severe infections (see section 4.4).
Patients in a severely immunocompromised state.
Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (see section 4.4 regarding other cardiovascular diseases).

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename of the administered product should be clearly recorded (or stated) in the patient file.

Progressive multifocal leukoencephalopathy
All patients treated with MabThera for rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis must be given the patient alert card with each infusion. The alert card

contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML).

Very rare cases of fatal PML have been reported following use of MabThera. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated.

If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML, the dosing of MabThera must be permanently discontinued. Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Infusion related reactions
MabThera is associated with infusionrelated reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumour lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of MabThera and can be observed with both formulations.

Severe infusionrelated reactions with fatal outcome have been reported during post-marketing use of the MabThera intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first MabThera IV infusion. They were characterized by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 4.8).

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have

been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Patients with a high tumour burden or with a high number (≥25 x 10^9/L) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with MabThera (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) see section 4.8. These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during MabThera administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the MabThera infusion.

Cardiac disorders
Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities
Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/L and/or platelet counts < 75 x 10^9/L as clinical experience in this population is limited. MabThera has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Regular full blood counts, including neutrophil and platelet counts, should be performed during MabThera therapy.

Infections
Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3).

Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

Cases of hepatitis B reactivation have been reported in subjects receiving MabThera including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that MabThera treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.
Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of MabThera in NHL and CLL (see section 4.8). The majority of patients had received MabThera in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Immunisations
The safety of immunisation with live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations. However with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received MabThera monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

Mean pre-therapeutic antibody titres against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera.

Skin reactions
Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis
Methotrexate (MTX) naïve populations with rheumatoid arthritis
The use of MabThera is not recommended in MTX-naïve patients since a favourable benefit risk relationship has not been established.

Infusion related reactions
MabThera is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered before each infusion of MabThera. In rheumatoid arthritis premedication with glucocorticoids should also be administered before each

infusion of MabThera in order to reduce the frequency and severity of IRRs (see section 4.2 and section 4.8).

Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials were mild to moderate in severity. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see section 4.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of MabThera infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue MabThera. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Medicinal products for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera.

There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, and those who experienced prior cardiopulmonary adverse reactions, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients closely monitored during administration. Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera infusion.

IRRs for patients with granulomatosis with polyangiitis and microscopic polyangiitis were similar to those seen for rheumatoid arthritis patients in clinical trials (*see section 4.8*).

Cardiac disorders
Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease should be monitored closely (see Infusion related reactions, above).

Infections
Based on the mechanism of action of MabThera and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following MabThera therapy (see section 5.1). Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g. hypogammaglobulinaemia (see section 4.8). It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera.

Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.

Very rare cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of MabThera for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and vasculitis.

Hepatitis B Infections
Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis patients receiving MabThera.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Late neutropenia
Measure blood neutrophils prior to each course of MabThera, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection (see section 4.8).

Skin reactions
Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event with a suspected relationship to MabThera, treatment should be permanently discontinued.

Immunisation
Physicians should review the patient's vaccination status and follow current immunisation guidelines prior to MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

The safety of immunisation with live viral vaccines following MabThera therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted.

Patients treated with MabThera may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised trial, patients with rheumatoid arthritis treated with MabThera and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47% vs. 93%), when given 6 months after MabThera as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera.

In the overall experience of MabThera repeat treatment over one year in rheumatoid arthritis, the proportions of patients with positive antibody titres against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Concomitant/sequential use of other DMARDs in rheumatoid arthritis
The concomitant use of MabThera and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.

There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following MabThera (see section 4.5). The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with MabThera, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following MabThera therapy.
Malignancy
Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MabThera in rheumatoid arthritis patients (see section 4.8) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

4.5 Interaction with other medicinal products and other forms of interaction

Currently, there are limited data on possible drug interactions with MabThera.
In CLL patients, co-administration with MabThera did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MabThera.

Co-administration with methotrexate had no effect on the pharmacokinetics of MabThera in rheumatoid arthritis patients.

Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following MabThera. In these patients the rate of clinically relevant infection while on MabThera was 6.01 per 100 patient years compared to 4.97 per 100 patient years following treatment with the biologic DMARD.

4.6 Fertility, pregnancy and lactation

<u>Contraception in males and females</u>
Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with MabThera.

<u>Pregnancy</u>
IgG immunoglobulins are known to cross the placental barrier.
B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. Similar effects have been observed in animal

studies (see section 5.3). For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.

Fertility
Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Summary of the safety profile
The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.
The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were IRRs which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of MabThera.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trials in patients with CLL.

The most frequent reported or observed serious adverse drug reactions were:
• IRRs (including cytokine-release syndrome, tumour-lysis syndrome), see section 4.4.
• Infections, see section 4.4.
• Cardiovascular events, see section 4.4.
Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

Tabulated list of adverse reactions
The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

Table 1 ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2] Pneumo-cystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombo-cytopenia	anaemia, +pancytopenia, +granulo-cytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymph-adenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions[4], angioedema	hyper-sensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombo-cytopenia[4]
Metabolism and nutrition disorders		hyper-glycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypo-calcaemia				
Psychiatric disorders			depression, nervousness,			

Nervous system disorders		paraesthesia, hypo-aesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		[+]myocardial infarction[4 and 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supra-ventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia	severe cardiac disorders [4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leuko-cytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Broncho-spasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4],	lung infiltration,
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia,	abdominal enlargement		gastro-intestinal perforation[7]	

		throat irritation				
Skin and subcutaneous tissue disorders	pruritus, rash, [+]alopecia	urticaria, sweating, night sweats, [+]skin disorder			severe bullous skin reactions, Stevens-Johnson syndrome toxic epidermal necrolysis (Lyell's syndrome) [7]	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever , chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported

[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL

[2] see also section infection below

[3] see also section haematologic adverse reactions below

[4] see also section infusion-related reactions below. Rarely fatal cases reported

[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy

[6] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache,

throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1% of patients by the eighth cycle of MabThera (containing) treatment.

Description of selected adverse reactions

Infections

MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.

Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation.There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% FC. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic adverse reactions

In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7 % of the patients. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4%) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below

$1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% of patients in the R-FC group compared to 9% of patients in the FC group.
In studies of MabThera in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular adverse reactions
Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischaemia) in 3% of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC, 3% FC) and in the relapsed/refractory study (4% R-FC, 4% FC).

Respiratory system
Cases of interstitial lung disease, some with fatal outcome have been reported.

Neurologic disorders
During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC, 4% FC) and in the relapsed/refractory study (3% R-FC, 3% FC).
Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal disorders
Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of non-Hodgkin lymphoma. In the majority of these cases, MabThera was administered with chemotherapy.

IgG levels
In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years).

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Skin and subcutaneous tissue disorders
Toxic Epidermal Necrolysis (Lyell syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Patient subpopulations - MabThera monotherapy
Elderly patients (≥ 65 years):
The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

Bulky disease
There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment
The percentage of patients reporting ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Patient subpopulations - MabThera combination therapy
Elderly patients (≥ 65 years)
The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL.

<u>Experience from rheumatoid arthritis</u>
<u>Summary of the safety profile</u>
The overall safety profile of MabThera in rheumatoid arthritis is based on data from patients from clinical trials and from post-marketing surveillance.

The safety profile of MabThera in patients with moderate to severe rheumatoid arthritis (RA) is summarized in the sections below. In clinical trials more than 3100 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2400 patients received two or more courses of treatment with over 1000 having received 5 or more courses. The safety information collected during post marketing experience reflects the expected adverse reaction profile as seen in clinical trials for MabThera (see section 4.4). Patients received 2 x 1000 mg of MabThera separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). MabThera infusions were administered after an intravenous infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The most frequent adverse reactions considered due to receipt of MabThera were IRRs. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for MabThera, progressive multifocal leukoencephalopathy (PML) (see section 4.4) and serum sickness-like reaction have been reported during post marketing experience.

Table 2 Summary of adverse drug reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving MabThera

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare
Infections and Infestations	upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B
Blood and lymphatic system disorders		neutropenia[1]		late neutropenia[2]	Serum sickness-like reaction
Cardiac Disorders				Angina pectoris, atrial fibrillation, heart failure, myocardial infarction	Atrial flutter
Immune System Disorders	[3]Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia,		[3]Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema,		
General disorders and administration site conditions					

	fatigue, oropharyngeal pain, peripheral oedema, erythema)		generalized pruritus, anaphylaxis, anaphylactoid reaction)		
Metabolism and Nutritional Disorders		hypercholesterolemia			
Nervous System disorders	headache	paraesthesia, migraine, dizziness, sciatica			
Skin and Subcutaneous Tissue Disorders		alopecia			Toxic Epidermal Necrolysis (Lyell's syndrome), Stevens-Johnson syndrome[5]
Psychiatric Disorders		depression, anxiety			
Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain			
Musculo skeletal disorders		arthralgia / musculoskeletal pain, osteoarthritis, bursitis			
Investigations	decreased IgM levels[4]	decreased IgG levels[4]			

[1] Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials
[2] Frequency category derived from post-marketing data.
[3] Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. IRRs may occur as a result of hypersensitivity and/or to the mechanism of action.
[4] Includes observations collected as part of routine laboratory monitoring.
[5] Includes fatal cases

Multiple courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs following first MabThera exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most frequent during the first treatment course), RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Infusion-related reactions

The most frequent ADRs following receipt of MabThera in clinical studies were IRRs (refer to Table 2). Among the 3189 patients treated with MabThera, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to

MabThera. The incidence of IRRs declined with subsequent infusions. In clinical trials fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see sections 4.2 and 4.4). Severe IRRs with fatal outcome have been reported in the post-marketing setting.

In a trial designed to evaluate the safety of a more rapid MabThera infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 2-hour intravenous infusion of MabThera. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed.

Description of selected adverse reactions

Infections

The overall rate of infection was approximately 94 per 100 patient years in MabThera treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotics was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of MabThera. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the MabThera arms compared to control arms.

Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of MabThera for the treatment of autoimmune diseases. This includes rheumatoid arthritis and off-label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and vasculitis.

In patients with non-Hodgkin's lymphoma receiving MabThera in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma). Reactivation of hepatitis B infection has also been very rarely reported in RA patients receiving MabThera (see Section 4.4).

Cardiovascular adverse reactions

Serious cardiac reactions were reported at a rate of 1.3 per 100 patient years in the MabThera treated patients compared to 1.3 per 100 patient years in placebo treated patients. The proportions of patients experiencing cardiac reactions (all or serious) did not increase over multiple courses.

Neurologic events

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Neutropenia

Events of neutropenia were observed with MabThera treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of MabThera (see section 4.4).

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of MabThera treated patients and 0.27% (2/731) of placebo patients developed severe neutropenia.

Neutropenic events, including severe late onset and persistent neutropenia, have been rarely reported in the post-marketing setting, some of which were associated with fatal infections.
Skin and subcutaneous tissue disorders

Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Laboratory abnormalities
Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with MabThera. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM (see section 4.4).

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Experience from granulomatosis with polyangiitis and microscopic polyangiitis
In the clinical trial in granulomatosis with polyangiitis and microscopic polyangitis, 99 patients were treated with MabThera (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (*see section 5.1).*
Tabulated list of adverse reactions
The ADRs listed in Table 3 were all adverse events which occurred at an incidence of ≥ 5% in the MabThera group.

Table 3 Adverse Drug Reactions occurring at 6-months in ≥ 5% of patients receiving MabThera, and at a higher frequency than the comparator group, in the pivotal clinical study.

Body System **Adverse event**	**Rituximab** **(n=99)**
Blood and lymphatic system disorders	
Thrombocytopenia	7%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Immune system disorders	
Cytokine release syndrome	5%
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%

Nasopharyngitis	5%
Investigations	
Decreased haemoglobin	6%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
Nervous system disorders	
Dizziness	10%
Tremor	10%
Psychiatric disorders	
Insomnia	14%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Skin and subcutaneous tissue disorders	
Acne	7%
Vascular disorders	
Hypertension	12%
Flushing	5%

Selected adverse drug reactions

Infusion related reactions

IRRs in the GPA and MPA clinical trial were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Ninety nine patients were treated with MabThera and 12% experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. MabThera was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

Infections

In the 99 MabThera patients, the overall rate of infection was approximately 237 per 100 patient years (95% CI 197 - 285) at the 6-month primary endpoint. Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the MabThera group was pneumonia at a frequency of 4%.

Malignancies
The incidence of malignancy in MabThera treated patients in the granulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2.00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis of standardized incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions
Cardiac events occurred at a rate of approximately 273 per 100 patient years (95% CI 149-470) at the 6-month primary endpoint. The rate of serious cardiac events was 2.1 per 100 patient years (95% CI 3 -15). The most frequently reported events were tachycardia (4%) and atrial fibrillation (3%) (see Section 4.4).

Neurologic events
Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported in autoimmune conditions. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Hepatitis-B reactivation
A small number of cases of hepatitis-B reactivation, some with fatal outcome, have been reported in granulomatosis with polyangiitis and microscopic polyangiitis patients receiving MabThera in the postmarketing setting.
Hypogammaglobulinaemia
Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in granulomatosis with polyangiitis and microscopic polyangiitis patients treated with MabThera. At 6 months, in the active-controlled, randomised, double-blind, multicenter, non-inferiority trial, in the MabThera group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.

Neutropenia
In the active-controlled, randomised, double-blind, multicenter, non-inferiority trial of MabThera in granulomatosis with polyangiitis and microscopic polyangiitis, 24% of patients in the MabThera group (single course) and 23% of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in MabThera-treated patients. The effect of multiple MabThera courses on the development of neutropenia in granulomatosis with polyangiitis and microscopic polyangiitis patients has not been studied in clinical trials.

Skin and subcutaneous tissue disorders
Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via (see details below).

Ireland
IMB Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

Malta
ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous MabThera formulation is available from clinical trials in humans. The highest intravenous dose of MabThera tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

In the postmarketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02
Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95 % of all B cell non-Hodgkin's lymphomas.

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion of the first dose of MabThera. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg MabThera separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether MabThera was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of MabThera. In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m^2, and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.

Clinical Experience in Non-Hodgkin's lymphoma and in chronic lymphocytic leukaemia

Follicular lymphoma

Monotherapy

Initial treatment, weekly for 4 doses In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m^2 of MabThera as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % (CI_{95} % 41 % - 56 %) with a 6 % complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12 %), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53 % vs. 38 %), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50 % vs. 22 %). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78 % versus 43 % in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera. A statistically significant correlation was noted between response rates and bone marrow involvement. 40 % of patients with bone marrow involvement responded compared to 59 % of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-centre, single-arm trial, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m^2 of MabThera as intravenous infusion weekly for eight doses. The ORR was 57 % (95% Confidence interval (CI); 41% – 73%; CR 14 %, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses
In pooled data from three trials, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥ 10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m2 of MabThera as intravenous infusion weekly for four doses. The ORR was 36 % (CI_{95} % 21 % – 51 %; CR 3 %, PR 33 %) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses
In a multi-centre, single-arm trial, 58 patients with relapsed or chemoresistant low grade or follicular B cell NHL, who had achieved an objective clinical response to a prior course of MabThera, were re-treated with 375 mg/m^2 of MabThera as intravenous infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38 % (CI_{95} % 26 % – 51 %; 10 % CR, 28 % PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

Initial treatment, in combination with chemotherapy
In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 -5) every 3 weeks for 8 cycles or MabThera 375 mg/m^2 in combination with CVP (R-CVP). MabThera was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher ($p< 0.0001$ Chi-Square test) in the R-CVP group (80.9 %) than the CVP group (57.2 %). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively ($p < 0.0001$, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test).

The difference between the treatment groups with respect to overall survival showed a significant clinical difference ($p=0.029$, log-rank test stratified by centre): survival rates at 53 months were 80.9 % for patients in the R-CVP group compared to 71.1 % for patients in the CVP group.

Results from three other randomised trials using MabThera in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarized in table 4.

Table 4 Summary of key results from four phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	OS rates, %
					Median TTP:	53-months

M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	14.7 33.6 P<0.0001	71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

EFS – Event Free Survival
TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time of the analyses

Maintenance therapy
Previously untreated follicular lymphoma In a prospective, open label, international, multi-centre, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to MabThera maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area given every 2 months until disease progression or for a maximum period of two years.
After a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 5).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (Table 5). The results of the primary analysis were confirmed with longer follow-up (median observation time: 48 months and 73 months), and have been added to Table 5 to show the comparison between the 25 and 48 and 73 month follow-up periods.

Table 5 Maintenance phase: overview of efficacy results MabThera vs. observation after 73 months median observation time (compared with results of primary analysis based on 25 months median observation time, and updated analysis based on 48 months median observation time)

	Observation N=513	**MabThera N=505**	**Log-rank P value**	**Risk reduction**
Primary Efficacy				

PFS (median)	48.5 months [*48.4 months*] (NR)	NR [*NR*] (NR)	<0.0001 [*<0.0001*] (<0.0001)	42% [*45%*] (50%)
Secondary Efficacy				
EFS (median)	48.4 months [*47.6 months*] (37.8 months)	NR [*NR*] (NR)	<0.0001 [*< 0.0001*] (< 0.0001)	39% [*42%*] (46%)
OS (median)	NR [*NR*] (NR)	NR [*NR*] (NR)	0.8959 [*0.9298*] (0.7246)	-2% [*-2%*] (11%)
TNLT (median)	71.0 months [*60.2 months*] (NR)	NR [*NR*] (NR)	<0.0001 [*<0.0001*] (0.0003)	37% [*39%*] (39%)
TNCT (median)	85.1 months [*NR*] (NR)	NR [*NR*] (NR)	0.0006 [*0.0006*] (0.0011)	30% [*34%*] (40%)
ORR*	60.7% [*60.7%*] (55.0%)	79.0% [*79.0%*] (74.0%)	<0.0001# [*<0.0001#*] (< 0.0001)	OR=2.43 [*OR=2.43*] (OR =2.33)
Complete Response (CR/CRu) rate*	52.7% [*52.7%*] (47.7%)	66.8% [*72.2%*] (66.8%)	<0.0001 [*<0.0001*] (< 0.0001)	OR=2.34 [*OR=2.34*] [(OR = 2.21)

*At end of maintenance/observation; # p values from chi-squared test
Main values correspond to 73 months median observation time, italicized values in brackets correspond to 48 months median observation time, and values in parentheses correspond to 25 months median observation time (primary analysis). PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: time to next chemotherapy treatment; ORR: overall response rate; NR: not reached at time of clinical cut-off, OR: odds ratio.
MabThera maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (<60 years, >= 60 years), FLIPI score (<=1, 2 or >= 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR,CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

Relapsed/Refractory follicular lymphoma
In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MabThera maintenance therapy (n=167) or observation (n=167). MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly

improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 6).

Table 6 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary Efficacy				
ORR[2)]	74 %	87 %	0.0003	Na
CR[2)]	16 %	29 %	0.0005	Na
PR[2)]	58 %	58 %	0.9449	Na

[1)] Estimates were calculated by hazard ratios
[2)] Last tumour response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: partial response

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with MabThera led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone ($p< 0.0001$ log-rank test).The median PFS was 42.2 months in the MabThera maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61 % with MabThera maintenance treatment when compared to observation (95 % CI; 45 %-72 %). Kaplan-Meier estimated progression-free rates at 12 months were 78 % in the MabThera maintenance group vs. 57 % in the observation group. An analysis of overall survival confirmed the significant benefit of MabThera maintenance over observation (p=0.0039 log-rank test). MabThera maintenance treatment reduced the risk of death by 56 % (95 % CI; 22 %-75 %).

Table 7 Maintenance phase: overview of efficacy results MabThera vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (N = 167)	MabThera (N=167)	Log-Rank p value	
Progression-free survival (PFS)	14.3	42.2	< 0.0001	61 %
Overall Survival	NR	NR	0.0039	56 %
Time to new lymphoma treatment Disease-free survival[a]	20.1 16.5	38.8 53.7	< 0.0001 0.0003	50 % 67 %
Subgroup Analysis PFS CHOP R-CHOP CR PR OS	 11.6 22.1 14.3 14.3	 37.5 51.9 52.8 37.8	 < 0.0001 0.0071 0.0008 < 0.0001	 71 % 46 % 64 % 54 %

CHOP	NR	NR	0.0348	55 %
R-CHOP	NR	NR	0.0482	56 %

NR: not reached; [a]: only applicable to patients achieving a CR

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 7). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Diffuse large B cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p = 0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41 %. At 24 months, estimates for overall survival were 68.2 % in the R-CHOP arm compared to 57.4 % in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32 %.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2 % in the R-CHOP group and 62.4 % in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical laboratory findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 356 patients evaluated for HACA, 1.1 % (4 patients) were positive.

Chronic lymphocytic leukaemia

In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or MabThera in combination with FC (R-FC). MabThera was administered at a dosage of 375 mg/m^2 during the first

cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of each subsequent treatment cycle. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) for the first-line study (Table 8a and Table 8b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 9) were analysed for efficacy.
In the first-line study, after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p < 0.0001$, log-rank test). The analysis of overall survival showed a significant benefit of R-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test) (Table 8a). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) (Table 8b).

Table 8a First-line treatment of chronic lymphocytic leukaemia
Overview of efficacy results for MabThera plus FC vs. FC alone - 48.1 months median observation time

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			**Risk Reduction**
	FC (N = 409)	**R-FC (N=408)**	**Log-Rank p value**	
Progression-free survival (PFS)	32.8	55.3	<0.0001	45%
Overall Survival	NR	NR	0.0319	27%
Event Free Survival	31.3	51.8	<0.0001	44%
Response rate (CR, nPR, or PR) CR rates	72.6% 16.9%	85.8% 36.0%	<0.0001 <0.0001	n.a. n.a.
Duration of response*	36.2	57.3	<0.0001	44%
Disease free survival (DFS)**	48.9	60.3	0.0520	31%
Time to new treatment	47.2	69.7	<0.0001	42%

Response rate and CR rates analysed using Chi-squared Test. NR: not reached; n.a.: not applicable
*: only applicable to patients achieving a CR, nPR, PR
**: only applicable to patients achieving a CR

Table 8b First-line treatment of chronic lymphocytic leukaemia
Hazard ratios of progression-free survival according to Binet stage (ITT) – 48.1 months median observation time

Progression-free survival (PFS)	**Number of patients**		**Hazard Ratio (95% CI)**	**p-value (Wald test, not adjusted)**
	FC	**R-FC**		
Binet stage A	22	18	0.39 (0.15; 0.98)	0.0442
Binet stage B	259	263	0.52 (0.41; 0.66)	<0.0001
Binet stage C	126	126	0.68 (0.49; 0.95)	0.0224

CI: Confidence Interval
In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group ($p=0.0002$, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.

Table 9 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for MabThera plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	FC (N = 276)	R-FC (N=276)	Log-Rank p value	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR) CR rates Duration of response * Disease free survival (DFS)** Time to new CLL treatment	58.0% 13.0% 27.6 42.2 34.2	69.9% 24.3% 39.6 39.6 NR	0.0034 0.0007 0.0252 0.8842 0.0024	n.a. n.a. 31% -6% 35%

Response rate and CR rates analysed using Chi-squared Test.
*: only applicable to patients achieving a CR, nPR, PR; NR: not reached n.a. not applicable
**: only applicable to patients achieving a CR;
Results from other supportive studies using MabThera in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of previously untreated and/or relapsed/refractory CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity). These studies support the use of MabThera with any chemotherapy.
Data in approximately 180 patients pre-treated with MabThera have demonstrated clinical benefit (including CR) and are supportive for MabThera re-treatment.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with MabThera in all subsets of the paediatric population with follicular lymphoma and chronic lymphocytic leukaemia. See Section 4.2 for information on paediatric use.

Clinical experience in rheumatoid arthritis
The efficacy and safety of MabThera in alleviating the symptoms and signs of rheumatoid arthritis in patients with an inadequate response to TNF-inhibitors was demonstrated in a pivotal randomised, controlled, double-blind, multicenter trial (Trial 1).

Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). MabThera was administered as two IV infusions separated by an interval of 15 days. Patients received 2 x 1000 mg intravenous infusions of MabThera or placebo in combination with MTX. All patients received concomitant 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of patients, from the original placebo group received MabThera between weeks 24 and 56, under an open label extension study protocol.

Trials of MabThera in patients with early arthritis (patients without prior methotrexate treatment and patients with an inadequate response to methotrexate, but not yet treated with TNF-alpha

inhibitors) have met their primary endpoints. MabThera is not indicated for these patients, since the safety data about long-term MabThera treatment are insufficient, in particular concerning the risk of development of malignancies and PML.

Disease activity outcomes
MabThera in combination with methotrexate significantly increased the proportion of patients achieving at least a 20 % improvement in ACR score compared with patients treated with methotrexate alone (Table 10). Across all development studies the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and C-Reactive Proteins (mg/dL).

Table 10 Clinical response outcomes at primary endpoint in Trial 1(ITT population)

	Outcome†	Placebo+MTX	MabThera+MTX (2 x 1000 mg)
Trial 1		N= 201	N= 298
	ACR20	36 (18%)	153 (51%)***
	ACR50	11 (5%)	80 (27%)***
	ACR70	3 (1%)	37 (12%)***
	EULAR Response (Good/Moderate)	44 (22%)	193 (65%)***
	Mean Change in DAS	-0.34	-1.83***

† Outcome at 24 weeks
Significant difference from placebo + MTX at the primary timepoint: ***p ≤ 0.0001
Patients treated with MabThera in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 9). Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more MabThera treated patients treated with MabThera and methotrexate compared to patients treated with methotrexate alone (Table 10).

Radiographic response
Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score.
In Trial 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving MabThera in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81 % received MabThera either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving the original MabThera/MTX treatment also had no erosive progression over 56 weeks (Table 11).

Table 11 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	MabThera+MTX 2 × 1000 mg

Trial 1	(n = 184)	(n = 273)
Mean Change from Baseline:		
Modified Total Sharp score	2.30	1.01*
Erosion Score	1.32	0.60*
Joint Space narrowing score	0.98	0.41**
Proportion of patients with no radiographic change	46%	53%, NS
Proportion of patients with no erosive change	52%	60%, NS

150 patients originally randomised to placebo + MTX in Trial 1 received at least one course of RTX + MTX by one year

* p <0.05, ** p < 0.001. Abbreviation: NS, non significant Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in Trial 1 demonstrated significantly reduced progression of structural joint damage in patients receiving MabThera in combination with methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Physical function and quality of life outcomes

Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with MabThera compared to patients treated with methotrexate alone. The proportions of MabThera treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among patients receiving methotrexate alone (Table 12).

Significant improvement in health related quality of life was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36. Further, a significantly higher proportion of patients achieved MCIDs for these scores (Table 12).

Table 12 Physical Function and Quality of Life outcomes at week 24 in Trial 1

Outcome†	Placebo+MTX	MabThera+MTX *(2 x 1000 mg)*
	n=201	n=298
Mean change in HAQ-DI	0.1	-0.4***
% HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5	-9.1***
	n=197	n=294
Mean Change in SF-36 PHS	0.9	5.8***
% SF-36 PHS MCID	13%	48%***
Mean Change in SF-36 MHS	1.3	4.7**
% SF-36 MHS MCID	20%	38%*

† Outcome at 24 weeks

Significant difference from placebo at the primary time point: * p < 0.05, **p < 0.001 ***p ≤ 0.0001

MCID HAQ-DI ≥0.22, MCID SF-36 PHS >5.42, MCID SF-36 MHS >6.33

Efficacy in autoantibody (RF and or anti-CCP) seropositive patients

Patients seropositive to Rheumatoid Factor (RF) and/or anti- Cyclic Citrullinated Peptide (anti-CCP) who were treated with MabThera in combination with methotrexate showed an enhanced response compared to patients negative to both.

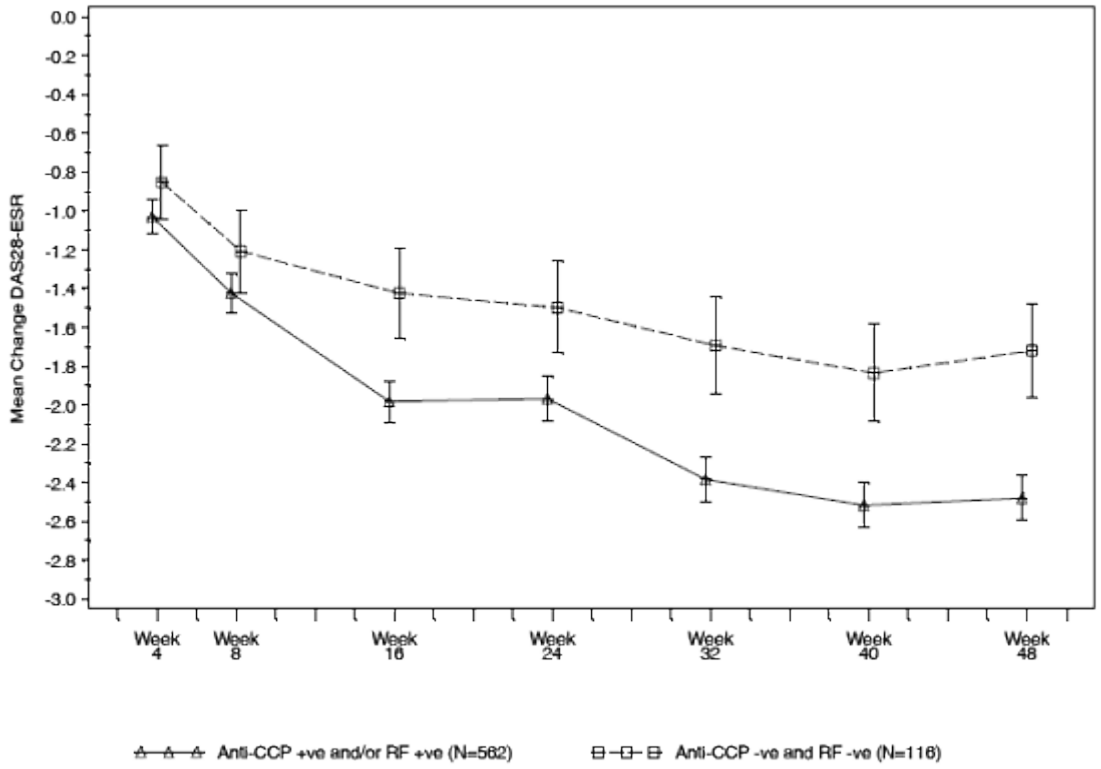
Efficacy outcomes in MabThera treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative patients (p=0.0312 and p=0.0096) (Table 13). These findings were replicated at Week 48, where autoantibody seropositivity also significantly increased the probability of achieving ACR70. At week 48 seropositive patients were 2-3 times more likely to achieve ACR responses compared to seronegative patients. Seropositive patients also had a significantly greater decrease in DAS28-ESR compared to seronegative patients (Figure 1).

Table 13 Summary of efficacy by baseline autoantibody status

	Week 24		**Week 48**	
	Seropositive (n=514)	**Seronegative (n=106)**	**Seropositive (n=506)**	**Seronegative (n=101)**
ACR20 (%)	62.3*	50.9	71. 1*	51.5
ACR50 (%)	32.7*	19.8	44.9**	22.8
ACR70 (%)	12.1	5.7	20.9*	6.9
EULAR Response (%)	74.8*	62.9	84.3*	72.3
Mean change DAS28-ESR	-1.97**	-1.50	-2.48***	-1.72

Significance levels were defined as ** p<0.05, **p<0.001, ***p<0.0001.*

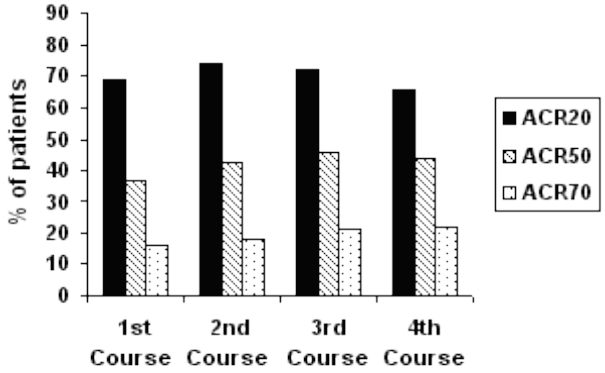
Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status



Long-term efficacy with multiple course therapy

Treatment with MabThera in combination with methotrexate over multiple courses resulted in sustained improvements in the clinical signs and symptoms of RA, as indicated by ACR, DAS28-ESR and EULAR responses which was evident in all patient populations studied (Figure 2). Sustained improvement in physical function as indicated by the HAQ-DI score and the proportion of patients achieving MCID for HAQ-DI were observed.

Figure 2: ACR responses for 4 treatment courses (24 weeks after each course (within patient, within visit) in patients with an inadequate response to TNF-inhibitors (n=146)



Clinical laboratory finding

A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for HACA in clinical studies following therapy with MabThera. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with MabThera in all subsets of the paediatric population with autoimmune arthritis. See Section 4.2 for information on paediatric use.

Clinical Experience in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis

A total of 197 patients aged 15 years or older with severely, active granulomatosis with polyangiitis (75%) and microscopic polyangiitis (24%) were enrolled and treated in an active-comparator, randomised, double-blind, multicenter, non-inferiority trial.

Patients were randomised in a 1:1 ratio to receive either oral cyclophosphamide daily (2mg/kg/day) for 3-6 months or MabThera (375 mg/m^2) once weekly for 4 weeks. All patients in the cyclophosphamide arm received azathioprine maintenance therapy in during follow-up. Patients in both arms received 1000mg of pulse intravenous (IV) methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of trial treatment.

The primary outcome measure was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The trial demonstrated non-inferiority of MabThera to cyclophosphamide for complete remission (CR) at 6 months (Table 14).

Efficacy was observed both for patients with newly diagnosed disease and for patients with relapsing disease (Table 15).

Table 14 Percentage of Patients Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population*)

	MabThera (n = 99)	**Cyclophosphamide (n = 98)**	**Treatment Difference (MabThera-Cyclophosphamide)**
Rate	63.6%	53.1%	10.6% 95.1%[b] CI (−3.2%, 24.3%) [a]

− CI = confidence interval.
− * Worst case imputation
[a] Non-inferiority was demonstrated since the lower bound (− 3.2%) was higher than the pre-determined non-inferiority margin (− 20%).
[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Table 15 Complete remission at 6-months by disease status

	MabThera	**Cyclophosphamide**	**Difference (CI 95%)**
All patients	n=99	n=98	
Newly diagnosed	n=48	n=48	
Relapsing	n=51	n=50	
Complete remission			
All Patients	63.6%	53.1%	10.6% (-3.2, 24.3)
Newly diagnosed	60.4%	64.6%	− 4.2% (− 23.6, 15.3)
Relapsing	66.7%	42.0%	24.7% (5.8, 43.6)

Worst case imputation is applied for patients with missing data

Complete Remission at 12 and 18 months
In the MabThera group, 48% of patients achieved CR at 12 months, and 39% of patients achieved CR at 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of complete remission), 39% of patients achieved CR at 12 months, and 33% of patients achieved CR at 18 months. From month 12 to month 18, 8 relapses were observed in the MabThera group compared with four in the cyclophosphamide group.

Retreatment with MabThera
Based upon investigator judgment, 15 patients received a second course of MabThera therapy for treatment of relapse of disease activity which occurred between 6 and 18 months after the first course of MabThera. The limited data from the present trial preclude any conclusions regarding the efficacy of subsequent courses of MabThera in patients with granulomatosis with polyangiitis and microscopic polyangiitis.

Continued immunosuppressive therapy may be especially appropriate in patients at risk for relapses (i.e. with history of earlier relapses and granulomatosis with polyangiitis, or patients with reconstitution of B-lymphocytes in addition to PR3-ANCA at monitoring). When remission with MabThera has been achieved, continued immunosuppressive therapy may be considered to prevent relapse. The efficacy and safety of MabThera in maintenance therapy has not been established.
Laboratory Evaluations

A total of 23/99 (23%) MabThera-treated patients in the trial tested positive for HACA by 18 months. None of the 99 MabThera-treated patients were HACA positive at screening. The clinical relevance of HACA formation in MabThera-treated patients is unclear.

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera as a single agent or in combination with CHOP therapy (applied MabThera doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of MabThera was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of MabThera in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of MabThera. This analysis suggests that dose adjustment of MabThera with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

MabThera, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4 doses to 203 patients with NHL naive to MabThera, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Upon administration of MabThera at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of MabThera when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with MabThera alone.

Chronic lymphocytic leukaemia

MabThera was administered as an intravenous infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (N=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/ m^2 infusion and the mean terminal half-life was 32 days (range, 14 – 62 days).

Rheumatoid arthritis

Following two intravenous infusions of MabThera at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 l (range, 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic

differences are not considered to be clinically relevant and dose adjustment is not required. No pharmacokinetic data are available in patients with hepatic or renal impairment.

The pharmacokinetics of rituximab were assessed following two intravenous (IV) doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 × 500 mg dose and ranged from 355 to 404 µg/mL for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1000 mg dose. C_{max} following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

The pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days.

Granulomatosis with polyangiitis and microscopic polyangiitis

Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m^2 MabThera once weekly for four doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0.313 L/day (range, 0.116 to 0.726 L/day) and 4.50 L (range 2.25 to 7.39 L) respectively. The PK parameters of rituximab in these patients appear similar to what has been observed in rheumatoid arthritis patients.

5.3 Preclinical safety data

Rituximab has shown to be highly specific to the CD20 antigen on B cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B cells in peripheral blood and in lymphoid tissue.

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post natally and was accompanied by a decrease in IgG level in the newborn animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunisation.
Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.

Specific studies to determine the effects of rituximab on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious effects on reproductive organs in males or females were observed.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium citrate
Polysorbate 80
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2 Incompatibilities

No incompatibilities between MabThera and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf life

30 months
The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature.
From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10mL vial: Clear Type I glass vials with butyl rubber stopper containing 100 mg of rituximab in 10 mL. Packs of 2 vials.
50mL vial: Clear Type I glass vials with butyl rubber stopper containing 500 mg of rituximab in 50 mL. Pack of 1 vial.

6.6 Special precautions for disposal and other handling

MabThera is provided in sterile, preservative-free, non-pyrogenic, single use vials.
Aseptically withdraw the necessary amount of MabThera, and dilute to a calculated concentration of 1 to 4 mg/mL rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection or 5% D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Roche Registration Limited
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United Kingdom

8. Marketing authorisation number(s)
EU/1/98/067/001
EU/1/98/067/002

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 2 June 1998
Date of latest renewal: 2 June 2008

10. Date of revision of the text
23 May 2014
Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

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Appendix 2. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the
18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Rep. Of South Africa, Oct. 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington USA, 2002 (Note of Clarification)
55th WMA General Assembly, Tokyo, Japan 2004 (Note of Clarification)
59th WMA General Assembly, Seoul, South Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must

take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give

informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating

suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix 3. Patient questionnaires

PBC-40

For each statement, please circle the response that comes closest to how you feel. If any of the statements do not apply to you please circle 'does not apply'.

Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?

1	I was able to eat what I liked	Never	Rarely	Sometimes	Most of the time	Always	
2	I ate or drank only a small amount, and still felt bloated	Never	Rarely	Sometimes	Most of the time	Always	Did not apply /never drink alcohol
3	I felt unwell when I drank alcohol	Never	Rarely	Sometimes	Most of the time	Always	

And IN THE LAST FOUR WEEKS, how often did you experience any of the following?

4	I had discomfort in my right side	Never	Rarely	Sometimes	Most of the time	Always
5	I had dry eyes	Never	Rarely	Sometimes	Most of the time	Always
6	My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always
7	I had aches in the long bones of my arms and legs	Never	Rarely	Sometimes	Most of the time	Always

Some people with PBC experience itching. How often did you experience itching IN THE LAST FOUR WEEKS? If you did not itch, please circle 'does not apply'

8	Itching disturbed my sleep	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/ no itch
9	I scratched so much I made my skin raw	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch
10	I felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch

Fatigue can also be a problem for many people with PBC. How often did the following statements apply to you IN THE LAST FOUR WEEKS?

11	I had to force myself to get out of bed	Never	Rarely	Sometimes	Most of the time	Always
12	I had to have a sleep during the day	Never	Rarely	Sometimes	Most of the time	Always
13	Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always
14	I felt worn out	Never	Rarely	Sometimes	Most of the time	Always
15	I felt so tired, I had to force myself to do the things I needed to do	Never	Rarely	Sometimes	Most of the time	Always
16	I felt so tired, I had to go to bed early	Never	Rarely	Sometimes	Most of the time	Always
17	Fatigue just suddenly hit me	Never	Rarely	Sometimes	Most of the time	Always
18	PBC drained every ounce of energy out of me	Never	Rarely	Sometimes	Most of the time	Always

The next section is about the effort and planning that can be involved in living with PBC. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?

19	Some days it took me a long time to do anything	Never	Rarely	Sometimes	Most of the time	Always
20	If I was busy one day I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always
21	I had to pace myself for day-to-day things	Never	Rarely	Sometimes	Most of the time	Always

The following statements are about the effects that PBC may have on things like memory and concentration. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?

22	Because of PBC I had to make a lot of effort to remember things	Never	Rarely	Sometimes	Most of the time	Always
23	Because of PBC I had difficulty remembering things from one day to the next	Never	Rarely	Sometimes	Most of the time	Always
24	My concentration span was short because of PBC	Never	Rarely	Sometimes	Most of the time	Always

25	Because of PBC, I had difficulty keeping up with conversations	Never	Rarely	Sometimes	Most of the time	Always
26	Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always
27	Because of PBC, I found it difficult to remember what I wanted to do	Never	Rarely	Sometimes	Most of the time	Always

Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?

28	Because of PBC, I get more stressed about things than I used to	Not at all	A little	Somewhat	Quite a bit	Very much	
29	My sex life has been affected because of PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
30	Having PBC gets me down	Not at all	A little	Somewhat	Quite a bit	Very much	
31	I feel I neglect my family because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
32	I feel guilty that I can't do what I used to do because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	
33	I worry about how my PBC will be in the future	Not at all	A little	Somewhat	Quite a bit	Very much	

These statements relate to the possible effects of PBC on your social life. Thinking of your own situation, how much do you agree or disagree with them?

34	I sometimes feel frustrated that I can't go out and enjoy myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
35	I tend to keep the fact that I have PBC to myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
36	I can't plan holidays because of having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
37	My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next section is about the impact that PBC may be having on your life overall. How much do you agree or disagree with the following statements?

38	Everything in my life is affected by PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
39	PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
40	I can still lead a normal life, despite having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next few questions are about your general health and well being:

A	In general, would you say your health is:	Excellent	Very good Good Fair Poor	Good	Fair	Poor
B	And how would you have rated it before you had PBC?	Excellent	Very good Good Fair Poor	Good	Fair	Poor
C	COMPARED TO ONE YEAR AGO, how would you rate your health in general now?	Much better	Somewhat better	About the same	Somewhat worse	Much worse

PROMIS HAQ

Please tell us about your ability to carry out your daily activities by placing a cross or tick in the box which best describes your abilities:

	Without difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Dress yourself, including buttons and shoelaces					
Shampoo your hair					
Stand up from an armless, straight chair					
Get in and out of bed					
Cut your food using cutlery					
Lift a full cup or glass to your mouth					
Open a new milk carton					
Walk the block on flat ground					
Climb up 5 stairs					
Wash and dry your body					
Have a bath					
Get on and off the toilet					
Reach up and take down a 5 pound object from above your head					
Bend down to pick clothing up off the floor					
Open a car door					
Open previously opened jars					
Turn taps on and off					
Run errands and shop					
Get in and out of a car					
Do household tasks such as vacuuming or gardening					

COGFAIL Questionnaire

The following questions concern your memory and concentration. Please circle how often you have trouble with each of the statements below.

		Very often	Quite often	Occasio-nally	Very rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0

		Very often	Quite often	Occasio-nally	Very rarely	Never
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

Epworth Sleepiness Scale (ESS)

The questions is this question are all about sleep and in particular about sleepiness in the daytime

Each question describes a normal routine daytime situation. See how likely you are to doze off or fall asleep in the following situations (in contrast to just feeling tired). Even if you have not done some of these things recently, just consider how they would have affect on you.

Please Select Only One Box Per Question.

1. Sitting and reading

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

2. Watching TV

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

3. Sitting, inactive in a public place (i.e. a meeting)

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

4. As a passenger in a car for an hour without a break

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

5. Lying down to rest in the afternoon when circumstances permit

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

6. Sitting and talking to someone

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

7. Sitting quietly after a lunch without alcohol

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

8. In a car while stopped for a few minutes in traffic

Would never doze off	**0**
Slight chance of dozing	**1**
Moderate chance of dozing	**2**
High chance of dozing	**3**

Orthostatic Grading Scale (OGS)

The questions in this section ask specifically about any dizziness you might have. Please tick the box that best describes your symptoms.

1. *Frequency of dizzy symptoms*

I *never or rarely* experience dizziness when I stand up	**0**
I *sometimes* experience dizziness when I stand up	**1**
I *often* experience dizziness when I stand up	**2**
I *usually* experience dizziness when I stand up	**3**
I *always* experience dizziness when I stand up	**4**

2. *Severity of dizzy symptoms*

I do not *experience dizziness when I stand up*	***0***
I experience mild *dizziness when I stand up*	***1***
I experience moderate *dizziness when I stand up and* sometimes *have to sit back down for relief*	***2***
I experience severe *dizziness when I stand up and* frequently *have to sit back down for relief*	***3***
I experience severe *dizziness when I stand up and* regularly faint *if I do not sit back down*	***4***

3. *Conditions under which orthostatic symptoms occur*

I never or rarely *experience dizziness under any circumstances*	***0***
I sometimes *experience dizziness under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (e.g. hot day, hot bath, hot shower)*	***1***
I often *experience dizziness under certain conditions, such as prolonged standing, a meal, exertion (e.g. walking), or when exposed to heat (e.g. hot day, hot bath, hot shower)*	***2***
I usually *experience dizziness under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (e.g. hot day, hot bath, hot shower)*	***3***
I always *experience dizziness when I stand up; the specific conditions do not matter*	***4***

4.*Activities of daily living*

My dizziness does not interfere *with activities of daily living (eg, work, chores, dressing, bathing)*	***0***
My dizziness mildly interferes *with activities of daily living (eg, work, chores, dressing, bathing)*	***1***
My dizziness moderately interferes *with activities of daily living (eg, work, chores, dressing, bathing)*	***2***
My dizziness *severely interfere*s with activities of daily living (eg, work, chores, dressing, bathing)	***3***
My dizziness *severely interfere*s with activities of daily living (eg, work, chores, dressing, bathing) *and I am in bed or a wheel chair because of it*.	***4***

5.*Standing time*

On most occasions, I can stand as long as necessary *without experiencing dizziness*	***0***
On most occasions, I can stand more than 15 minutes *before experiencing dizziness*	***1***
On most occasions, I can stand 5-14 minutes *before experiencing dizziness*	***2***
On most occasions, I can stand 1-4 minutes *before experiencing dizziness*	***3***
On most occasions, I can stand less than 1 minute *before experiencing dizziness*	***4***

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name:_____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

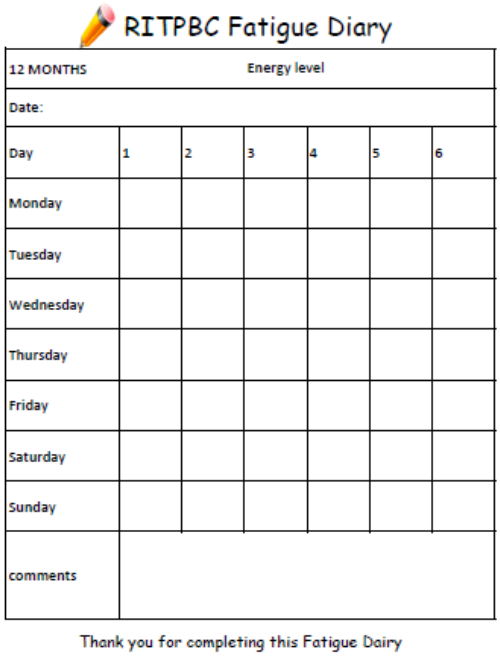
A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Not at all		
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

A D

TOTAL | | |

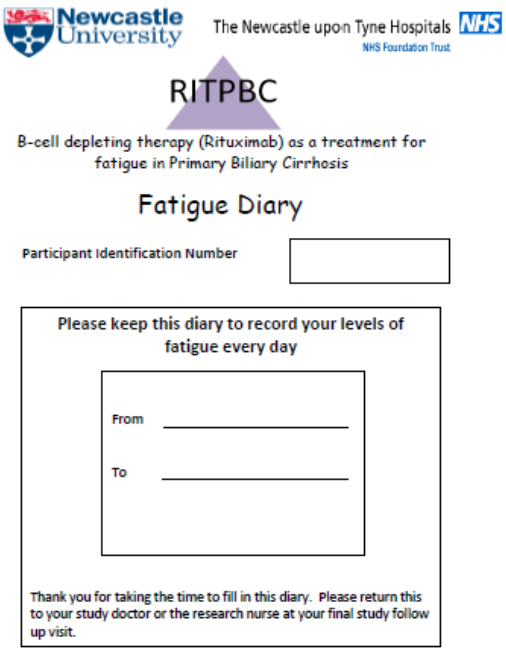
Appendix 4. Fatigue Diary



RITPBC Fatigue Diary

12 MONTHS	Energy level					
Date:						
Day	1	2	3	4	5	6
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
comments						

Thank you for completing this Fatigue Dairy



Newcastle University

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

RITPBC

B-cell depleting therapy (Rituximab) as a treatment for fatigue in Primary Biliary Cirrhosis

Fatigue Diary

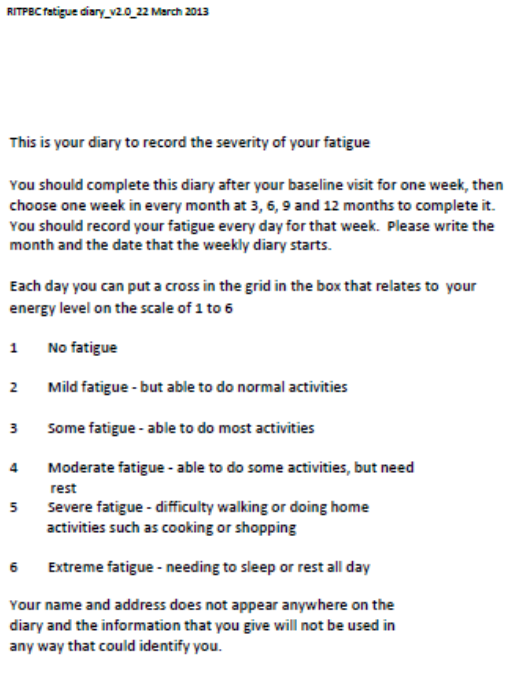
Participant Identification Number

Please keep this diary to record your levels of fatigue every day

From _____

To _____

Thank you for taking the time to fill in this diary. Please return this to your study doctor or the research nurse at your final study follow up visit.



RITPBC fatigue diary_v2.0_22 March 2013

This is your diary to record the severity of your fatigue

You should complete this diary after your baseline visit for one week, then choose one week in every month at 3, 6, 9 and 12 months to complete it. You should record your fatigue every day for that week. Please write the month and the date that the weekly diary starts.

Each day you can put a cross in the grid in the box that relates to your energy level on the scale of 1 to 6

1 No fatigue

2 Mild fatigue - but able to do normal activities

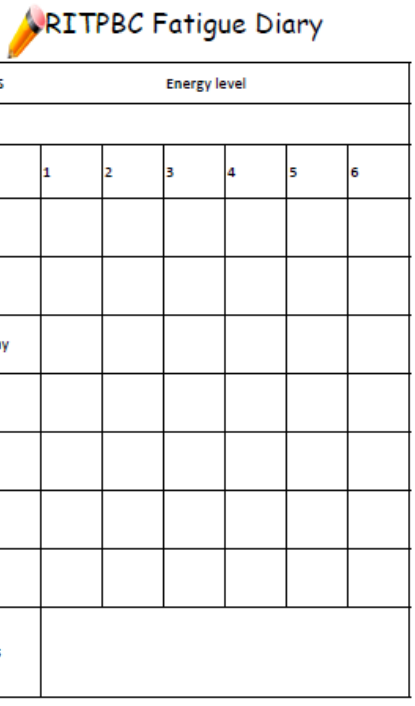
3 Some fatigue - able to do most activities

4 Moderate fatigue - able to do some activities, but need rest

5 Severe fatigue - difficulty walking or doing home activities such as cooking or shopping

6 Extreme fatigue - needing to sleep or rest all day

Your name and address does not appear anywhere on the diary and the information that you give will not be used in any way that could identify you.



RITPBC Fatigue Diary

9 MONTHS	Energy level					
Date:						
Day	1	2	3	4	5	6
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
comments						

RITPBC Fatigue Diary

6 MONTHS	Energy level					
Date:						
Day	1	2	3	4	5	6
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
comments						

RITPBC Fatigue Diary

BASELINE	Energy level					
Date:						
Day	1	2	3	4	5	6
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
comments						

RITPBC Fatigue Diary

1 MONTH	Energy level					
Date:						
Day	1	2	3	4	5	6
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
comments						

RITPBC Fatigue Diary

3 MONTHS	Energy level					
Date:						
Day	1	2	3	4	5	6
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						
comments						

Appendix 5. Clinical Research Facility Rituximab infusion guidelines

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Rituximab Infusion – Day 1

Study:.....

Patient Study Number:.....

Date:.....

N.B. This document is ONLY for use when a 1g dose of Rituximab is administered as a 4mg/ml intravenous infusion (total infusion volume 250ml), over a predicted time of 4hrs 15 mins (assuming no reduction of flow rate is necessary due to infusion related symptoms).

Pre-medication

Premedication	Dose	Route of administration	Time Started	Time Finished	Notes
Paracetamol	1g	Oral			To be given 1 hour prior to rituximab
Chlorphenamine	4mg	Oral			
Methylprednisolone	100mg (in 100ml bag 0.9% sodium chloride)	IV infusion over 30 mins.			Administration must be completed at least 30 minutes prior to rituximab

Rituximab infusion

Medication	Dose	Route of administration	Time Started	Time Finished	Notes
Rituximab	1g	IV infusion			To be administered as per infusion rates chart below

Rituximab infusion rate:

(Final concentration - Rituximab 4mg/ml in 0.9% sodium chloride)

Actual Time	Time (mins)	Infusion Rate * (ml/hour)	Infusion Rate * (mg/hour)	Cumulative dose	
				mg	ml
	0-30	**12.5**	50	25	6.25
	31-60	**25**	100	75	18.75
	61-90	**37.5**	150	150	37.5
	91-120	**50**	200	250	62.5
	121-150	**62.5**	250	375	93.75
	151-180	**75**	300	525	131.25
	181-210	**87.5**	350	700	175
	211-240	**100**	400	900	225
	241-255	**100**	400	1000	250

*Assuming that no reduction in flow rate is necessary due to infusion related symptoms

CRF Rituximab infusion chart version 2.3 (final), dated 29.11.2012
Author: K. Walker

Rituximab Infusion - Day 1 continued
Observations during rituximab infusion

Time (mins)	Actual time	BP (mm Hg)	Pulse/min	Temp (°C)	Respirations/min
Pre dose					
15					
30					
45					
60					
90					
120					
150					
180					
210					
240					

Observations - post rituximab infusion Time rituximab infusion completed: _____

Time (mins)	BP (mm Hg)	Pulse/min	Temp (°C)	Respirations/min
30 mins post				
60 mins post				

	NAME	SIGNATURE	DATE
Prepared by (Nurse)	KATHRYN WALKER		7 DEC 2012
Approved by (Pharmacist)	G.H.R.H.	J.J.	10 Dec '12.
Approved by (Doctor)	GILLIAN BELL		7 DEC 2012

CRF Rituximab infusion chart version 2.3 (final), dated 29.11.2012
Author: K. Walker

Rituximab Infusion – Day 15

Study:.....

Patient Study Number:.....

Date:.....

N.B. This document is ONLY for use when a 1g dose of Rituximab is administered as a 4mg/ml intravenous infusion (total infusion volume 250ml), over a predicted time of 3hrs 15 mins (assuming no reduction of flow rate is necessary due to infusion related symptoms).

Pre-medication

Premedication	Dose	Route of administration	Time		Notes
			Started	Finished	
Paracetamol	1g	Oral			To be given 1 hour prior to rituximab
Chlorphenamine	4mg	Oral			
Methylprednisolone	100mg (in 100ml bag 0.9% sodium chloride)	IV infusion over 30 mins.			Administration must be completed at least 30 minutes prior to rituximab

Rituximab infusion

Medication	Dose	Route of administration	Time		Notes
			Started	Finished	
Rituximab	1g	IV infusion			To be administered as per infusion rates chart below

Rituximab infusion rate:

(Final concentration - Rituximab 4mg/ml in 0.9% sodium chloride as per local guidelines)

Actual Time	Time (mins)	Infusion Rate * (ml/hour)	Infusion Rate * (mg/hour)	Cumulative dose	
				mg	ml
	0-30	**25**	100	50	12.5
	31-60	**50**	200	150	37.5
	61-90	**75**	300	300	75
	91-120	**100**	400	500	125
	121-150	**100**	400	700	175
	151-180	**100**	400	900	225
	181-195	**100**	400	1000	250

*Assuming that no reduction in flow rate is necessary due to infusion related symptoms

CRF Rituximab infusion chart version 2.3 (final), dated 29.11.2012
Author: K. Walker

Rituximab Infusion - Day 15 continued
Observations during rituximab infusion

Time (mins)	Actual time	BP (mm Hg)	Pulse/min	Temp (°C)	Respirations/min
Pre dose					
15					
30					
45					
60					
90					
120					
150					
180					

Observations - post rituximab infusion Time rituximab infusion completed: _____

Time (mins)	BP (mm Hg)	Pulse/min	Temp (°C)	Respirations/min
30 mins post				
60 mins post				

	NAME	SIGNATURE	DATE
Prepared by (Nurse)	KATHRYN WALKER		7 DEC 2012
Approved by (Pharmacist)	[illegible]	[illegible]	10 Dec '12
Approved by (Doctor)	GILLIAN BELL		7 DEC 2012

CRF Rituximab infusion chart version 2.3 (final), dated 29.11.2012
Author: K. Walker

Appendix 6. Trial Steering Committee Terms of Reference

The Trial Steering Committee (TSC) will consist of:

Dr Roger Chapman	-	Chair
Dr Jo Nijs	-	Independent member
Joan Bedlington	-	Lay member
Dr Mark Swain	-	Independent member
Professor David Jones	-	Chief Investigator
Professor Julia Newton	-	Co-Investigator
Denise Howel	-	Trial Statistician
Dr Jennifer Wilkinson	-	Senior Trial Manager
Dr Alison Steel	-	Trial Manager

Overall role of the TSC

The role of the TSC is to provide overall independent supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to rigorous standards. The safety, rights and well-being of the trial participants are paramount.

Specific roles and responsibilities

1. The responsibility for calling and organising TSC meetings lies with the Chief Investigator in association with the Chair of the TSC.

2. The TSC will meet three times during the running of this three year study but additional meetings can be convened if considered necessary. TSC meetings will be in person or by teleconference.

3. Meetings will be minuted by the project team.

4. Minutes must be made available to the Trial Sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) and Funder (EME) if required.

5. The project team will provide the TSC with a study report in advance of any meetings.

6. The content of the study report will focus on trial progress and conduct.

7. The TSC chairperson will be responsible for conduct of TSC.

8. In the case of a major decision, every effort should be made for the TSC to reach a unanimous decision. If the committee cannot reach a decision, a vote may be taken. If necessary, the chairperson has the deciding vote.

9. The TSC will also:
    a. Receive and consider feedback or recommendations from the DMEC
    b. Comment on and approve any proposed substantial amendments to the trial
    c. Comment on and approve the trial results dissemination strategy
    d. Oversee the timely reporting of the trial results

10. Any recommendation of the DMEC to discontinue or temporarily suspend study recruitment will be immediately enacted by the TSC.

The main features of the TSC are as follows:

- The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the trial is the responsibility of the Investigators and the Chief Investigator may wish to set up a separate Trial Management Group (TMG) to assist with this function.

- In particular, the TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question.

- The safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.

- The TSC should provide advice, through its Chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial.

- Membership of the TSC should be limited and include an independent Chair[1], at least two other independent members, one or two Principal Investigators and, where possible, a consumer representative. Involvement of independent members provides protection for both Trial Participants and the Principal Investigator(s).

- Representatives of the Trial Sponsor and the Trial Funder should be invited to all TSC meetings.

- Responsibility for calling and organising TSC meetings lies with the Chief Investigator. The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.

- There may be occasions when the Trial Sponsor or the Trial Funder will wish to organise and administer these meetings for particular trials.

- The TSC will provide evidence to support any requests for extensions, indicating that all practicable steps have been taken to achieve targets.

[1]The Good Clinical Practice (GCP) guidelines define independence as: 'not involved directly in the trial other than as a member of the TSC'.

Appendix 7. Data Monitoring and Ethics Committee Terms of Reference

The Data Monitoring and Ethics Committee (DMEC) will consist of:

Professor Mark Thursz - Independent chair
Dr Paul Baxter - Independent statistician
Dr Gideon Hirschfield - Independent expert

The main features of the DMEC are as follows:

- It is the only body involved in a trial that has access to the unblinded comparative data.
- The role of its members is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue.
- The safety, rights and well-being of the trial participants are paramount.
- The DMEC considers whether any interim analysis is necessary, considers the data from any analysis and considers requests for its release, then advises the TSC.
- The DMEC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies.
- If funding is required above the level originally requested, the DMEC may be asked by the Chief Investigator, TSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not unblind the trial.
- Membership of the DMEC should be completely independent, small (3-4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statisticians.
- Responsibility for calling and organising DMEC meetings lies with the Chief Investigator, in association with the Chair of the DMEC. The project team should provide the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC.
- The DMEC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be feed into the TSC.
- Research Governance Framework information is available on from the Department of Health (DoH) website on: http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/fs/en
- The MRC Guidelines for GCP are available on: http://www.mrc.ac.uk/pdf-ctg.pdf including suggested committee terms of reference and draft templates for agendas, reports, etc.