EudraCT number	2021-004283-10	**Version and Date**	v 3.0	14-Jul-2022
Title	A Global Study of Novel Agents in Paediatric and Adolescent Relapsed and Refractory B-cell non-Hodgkin Lymphoma (B-NHL)			
Abbreviated title	Glo-BNHL			
Sponsor	University of Birmingham			
Chief Investigator	Dr Amos Burke, Cambridge University Hospitals NHS Foundation Trust			
Trials Unit	Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham CRCTU Senior Biostatistician and Co-investigator: Prof Lucinda Billingham Co-Investigator: Dr Emma Seaford CRCTU Team Leader: Mrs Anna Lawson			
Glossary of terms	ADC – Antibody-Drug Conjugate ALT - Alanine aminotransferase ANC - Absolute neutrophil count AST - Aspartate aminotransferase B-NHL - B-cell Non Hodgkin Lymphoma BsAb – Bispecific Antibody CAR T-cells – Chimeric Antigen Receptor T-cells CNS – Central nervous system CR – Complete response CRCTU – Cancer Research Clinical Trials Unit CT - Computerised tomography DLBCL - Diffuse Large B-Cell Lymphoma EFS – Event free survival time GFR - Glomerular filtration rate HSCT - Haematopoietic stem cell transplantation MRI - Magnetic resonance imaging NCI CTCAE - National Cancer Institute Common Terminology Criteria for Adverse Events NOS - Not Otherwise Specified OR – Objective response OS – Overall survival time PD – Progressive disease PFS - Progression free survival time PMLBL - primary mediastinal large B-cell lymphoma PR – Partial response R-ICE – Rituximab, ifosfamide, carboplatin, etoposide SD – Stable disease ULN – Upper limit of normal			
Planned number of centres	Total = 45 (Europe = 30; International = 15)			
Indication	Relapsed/Refractory paediatric and adolescent mature B-NHL			

Primary objective ***(see the evaluation criteria below)***	• **<u>Treatment Arm I: Bispecific Antibody (BsAb):</u>** Estimate the clinical efficacy of BsAb treatment in patients with relapsed/refractory B-NHL in either first (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy). • **<u>Treatment Arm II: Antibody-drug conjugate (ADC) with standard chemotherapy</u>**: Estimate the clinical efficacy of an ADC treatment with modified R-ICE chemotherapy in patients with relapsed/refractory B-NHL in first (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy). • **<u>Treatment Arm III: Chimeric antigen receptor</u> (<u>CAR) T-cells</u>:** Estimate the efficacy of CAR T-cell therapy in patients who have CAR T-cell product available.
Secondary Objectives ***(see the evaluation criteria below)***	• Assess the safety profile of the novel agent in children, adolescents and young adults • Determine the pharmacokinetics of the novel agent at the recommended trial dose in children, adolescents and young people, where relevant • Any other treatment arm specific objectives (e.g. assess the relevant pharmacodynamic markers for the novel agent). These will be detailed in the relevant treatment arm sections of the protocol
Primary evaluation criterion	• **<u>Treatment Arm I: BsAb</u>:** Occurrence of an objective response ((OR) i.e. Complete Response (CR) or PR as their best response (timeframe will be dependent on the drug being investigated) assessed according to International Paediatric Non-Hodgkin Lymphoma Response Criteria) • **<u>Treatment Arm II: ADC with standard chemotherapy</u>:** Occurrence of CR following a maximum of three cycles of treatment • **<u>Treatment Arm III: CAR T-cells</u>:** Occurrence of OR following CAR T-cell infusion
Secondary evaluation criteria	• Event-free survival time (EFS) • Progression free survival time (PFS) • Overall survival time (OS) • Incidence of Adverse Events of Special Interest (AESI) • Pharmacokinetic profile of novel agent, where relevant • Pharmacodynamics markers, where relevant •

Study methodology	Prospective, non-randomised platform trial with a Bayesian design evaluating novel therapies in three parallel arms: **<u>Treatment Arm I: BsAb</u>:** **Population:** Children, adolescents and young adults with relapsed/refractory* B-NHL in first relapse (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy), including those achieving insufficient response (partial response (PR), stable disease (SD) or progressive disease (PD)) to ADC with standard chemotherapy to progress to HSCT or those without available CAR T-cells **<u>Treatment arm II: ADC with standard chemotherapy:</u>** **Population:** Children, adolescents and young adults with relapsed/refractory* B-NHL in first relapse (only one prior line of therapy) or subsequent (more than one prior line of therapy relapse), including those achieving insufficient response PR, SD or PD) to BsAb therapy to progress to HSCT or those without available CAR T-cells **<u>Treatment arm III: CAR T-cells:</u>** **Population:** Children, adolescents and young adults with relapsed/refractory* B-NHL who have had insufficient response (PR, SD, PD to prior therapy to progress to HSCT) and have CAR T-cell product available Patients may be eligible to enter more than one treatment arm during the lifetime of the platform study. Please see the patient flow schema in Appendix 1 for further information. ***Refractory disease** The following patients are considered to have refractory disease and can be included in this trial: • Patients who do not achieve PR or CR with last therapy • Patients with partial response to last therapy (biopsy proven), with no evidence of progression.

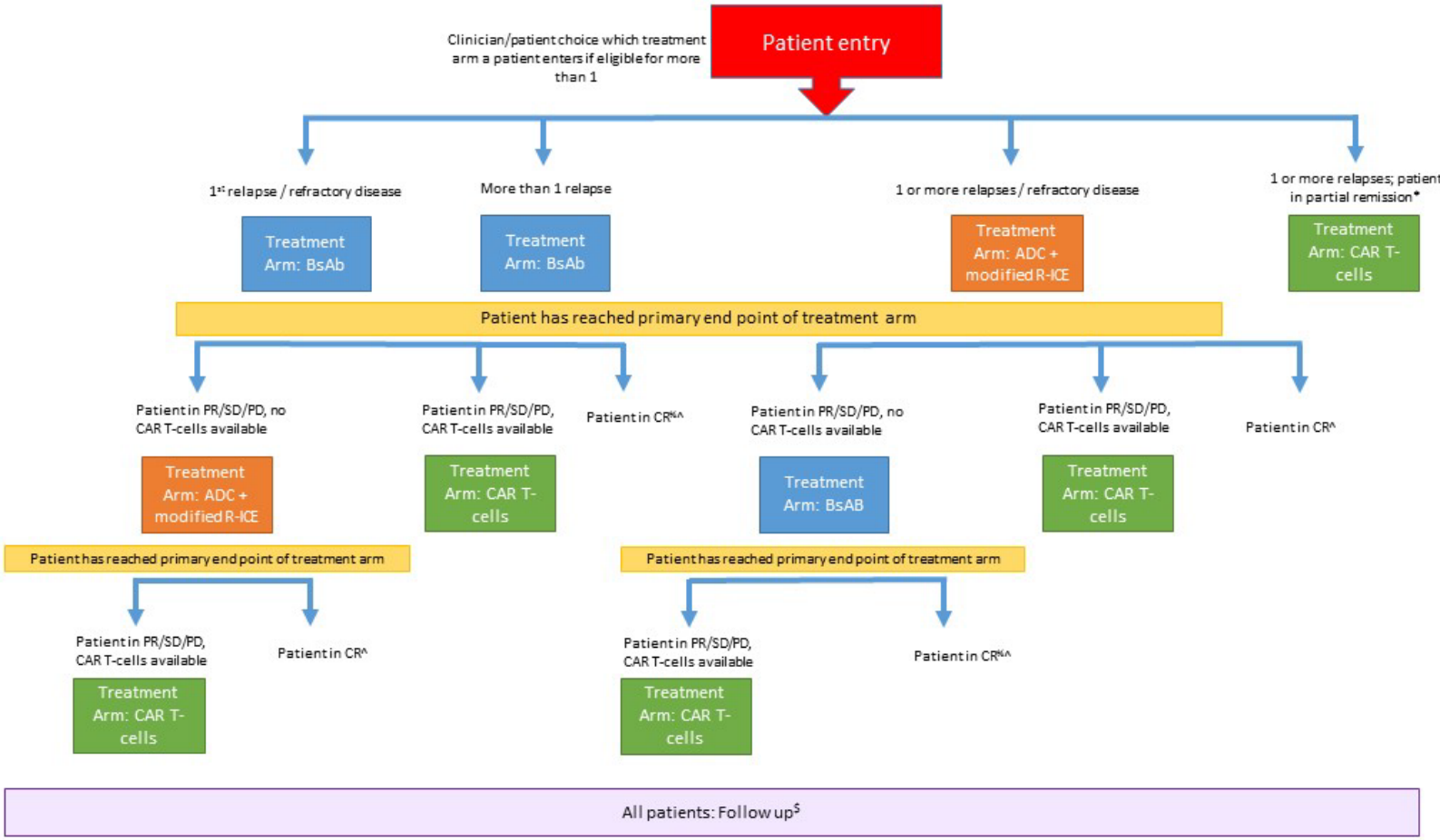
Eligibility Criteria	Each treatment arm will have additional specific inclusion and exclusion criteria.
	
	Glo-BNHL inclusion criteria (applicable to all treatment arms):
	• Histologically proven mature B-NHL (Diffuse Large B-Cell Lymphoma (DLBCL), Burkitt Lymphoma/Leukemia or atypical Burkitt/Burkitt-like lymphoma, primary mediastinal large B-cell lymphoma (PMLBL) and mature B-NHL/Not Otherwise Specified (NOS)) at initial diagnosis
	• Radiologically and/or histologically proven B-NHL in first relapse (only one prior line of therapy) or subsequent relapse (more than one prior line of therapy) or refractory B-NHL. (Note: relapses following prior targeted therapy must be histologically proven to confirm target positivity).
	• If relapse occurs more than two years after previous therapy, a biopsy must be performed
	• Evaluable disease as per the international paediatric NHL response criteria, including:
	  ○ at least one bi-dimensionally measurable nodal lesion >1.5 cm in its longest dimension;
	  ○ or at least one bi-dimensionally measurable extra-nodal lesion > 1.0 cm in its longest dimension on CT or MRI;
	  ○ or bone marrow involvement (≥25% involvement from bone marrow, if only site of disease);
	  ○ or evaluable CNS disease (evaluable by imaging or Cerebrospinal Fluid (CSF) analysis)
	• Age ≥6 months and <25 years old at the time of study registration
	• Performance status ≥50 using Karnofsky or Lansky performance scores
	• Life expectancy ≥8 weeks
	• Adequate bone marrow function documented by at least:
	  ○ Platelet count ≥50 x 10^9/L (no platelet transfusion therapy within 3 days prior to treatment), unless bone marrow involvement**
	  ○ Absolute neutrophil count (ANC) ≥ 0.75 x 10^9/L (no granulocyte colony stimulating factor within 2 days prior to treatment), unless bone marrow involvement**
	• Adequate hepatic function documented by at least:
	  ○ Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) with a total bilirubin ≤ 1.5 x ULN
	  ▪ In the presence of lymphoma infiltration of the liver, patients must have AST and/or ALT of ≤ 5 x ULN with a total bilirubin ≤ 1.5 x ULN
	  ○ Total bilirubin ≤1.5 X ULN

	▪ Patients with known Gilbert syndrome will be excluded if the total bilirubin value is >4 x ULN for the local general population. • Documented negative pregnancy test for female patients of childbearing potential within seven days prior to trial entry • Patients of childbearing potential agrees to use effective contraception whilst on study treatment and for 12 months following treatment discontinuation • Written informed consent given by patient and/or parents/legal representative **<u>** Bone marrow involvement</u>** Patients who have ≥ 25% blasts in the bone marrow are considered to have bone marrow involvement. Requirements for bone marrow function do not apply to these patients. **Glo-BNHL exclusion criteria (applicable to all treatment arms):** • B-cell Acute Lymphoblastic Leukaemia (B-ALL)/B-cell Lymphoblastic Lymphoma (B-LBL) • Patients within 90 days of an allogenic HSCT procedure • Patients within 45 days of an autologous HSCT procedure • Patients who have experienced graft versus host disease (GvHD) requiring therapy, and/or immunosuppressive treatment • Patients within 42 days of any CAR T-cell therapy or other cellular therapies • Patients with known DNA repair disorder or known primary immunodeficiency • Patients who are pregnant or breastfeeding • Patients who cannot regularly be followed up due to psychological, social, geographical or other issues • Patients for whom non-compliance with treatment or study procedures is expected • Uncontrolled concomitant infection. Severe infection (such as sepsis, pneumonia, etc.) should be clinically controlled at the time of trial entry. • Positive HIV serology • Severe active viral infection, especially hepatitis B and/or C. • Hepatitis B carrier status history of Hepatitis B Virus or positive serology. A patient is considered as Hepatitis B Virus carrier or to have (had) Hepatitis B Virus infection in case of: - Unimmunised and HBsAg and/or anti-HBs antibody and/or anti- HBc antibody positive - Immunised and HBsAG and/or anti-HBc antibody positive • Previous investigational treatment within 14 days of first dose • Live vaccine within 28 days prior to trial entry

	• Known history of hypersensitivity to any of the treatments or excipients
Translational research studies	There will be prospective sample collection for an embedded biological study and further biological studies throughout the lifetime of the platform. Further details to follow.
Evaluation during treatment and follow-up	Response assessment will follow the international paediatric NHL response criteria. Others – to be confirmed.
Statistical methodology and sample size determination	The trial will use a Bayesian approach to estimation and decision-making in each treatment arm. The statistical analysis plan will be a simple beta-binomial conjugate analysis combining the observed trial data with a minimally-informative prior distribution. The posterior probability distribution will be used to: (i) estimate the true efficacy rate with 95% credible intervals to indicate the level of uncertainty and (ii) determine whether the probability that the true efficacy rate is greater than a clinically relevant critical value is sufficiently high (>0.80) to declare the treatment worthy of consideration (referred to as a GO decision). The target sample size is at least 15 patients in each treatment arm (or sub-group). Interim analyses to allow early stopping for futility are planned. At these stopping points, the posterior probability distribution will be used to calculate the predicted probability of success given the current observed data, where success is a GO decision at final analysis. The target sample size of 15 patients in each treatment arm is sufficient to provide initial robust decision-making (see below for specific details relating to each treatment arm). Should a treatment arm be declared worthy of further consideration based on the analysis of 15 patients, then there will be an option to expand the cohort to a larger number to provide evidence to support a marketing authorisation application. **<u>Treatment Arm I: BsAb</u>:** **Sub-group A:** For patients with first relapse (only one prior line of therapy) or refractory disease, the clinically meaningful OR rate is 40%. With 15 patients, the trial would have 0.05 probability of an incorrect GO decision when the true OR rate is 30% and 0.79 probability of a correct GO decision when the true OR rate is 60%. A GO decision would occur with an observed OR rate of 8/15 (Bayesian estimate 53%) patients. **Sub-group B:** For patients with subsequent relapse (more than one prior line of therapy), the clinically meaningful OR rate is 10%. With 15 patients, the

	trial would have 0.04 probability of an incorrect GO decision when the true OR rate is 5% and 0.87 probability of a correct GO decision when the true OR rate is 30%. A GO decision would occur with an observed OR rate of 3/15 (Bayesian estimate 20%) patients. **Treatment arm II: ADC with standard chemotherapy:** The clinically meaningful CR rate is 20%. With 15 patients, the trial would have 0.01 probability of an incorrect GO decision when the true CR rate is 10% and 0.76 probability of a correct GO decision when the true CR rate is 40%. A GO decision would occur with an observed CR rate of 5/15 (Bayesian estimate 35%) patients. **Treatment arm III: CAR T-cells:** The clinically meaningful OR rate is 10%. With at least 15 patients, the trial would have 0.04 probability of an incorrect GO decision when the true OR rate is 5% and 0.87 probability of a correct GO decision when the true OR rate is 30%. A GO decision would occur with an observed OR rate of 3/15 (Bayesian estimate 20%) patients.	
Number of patients	30 patients per year with recruitment for 7 years. Total: 210	
Duration of the trial	**Planned start:** 2022	
	Treatment: Dependent on treatment arm (see Treatment section above)	
	Post-treatment follow-up within the study: minimum 2 years	
	Duration of the study: 7 years	Planned end enrolment: 2029 Planned study end: 2032

Appendix 1 : Patient pathway



*Dependent on agent in treatment arm – specified in protocol

$Continue to follow up patient and report any subsequent treatment data

%Patient may stay on treatment – as defined in protocol

^Patients in CR may receive HSCT and will continue to be followed up

Glo-BNHL Patient Flow Schema
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