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**ACCEPT**

**A Phase Ib/II combination of acalabrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) for patient Diffuse Large B-cell Lymphoma (DLBCL)**

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**COORDINATING CENTRE:** Southampton Clinical Trials Unit

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## FUNDER

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**Protocol Information**

This protocol describes the ACCEPT trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

**Compliance**

This trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, in accordance with current Data Protection Regulations and all other regulatory requirements, as appropriate.

# TABLE OF CONTENTS

LIST OF ABBREVIATIONS	7
KEYWORDS	8
TRIAL SYNOPSIS	9
TRIAL SCHEMA	12
SCHEDULE OF OBSERVATIONS AND PROCEDURES	14
<b>1 INTRODUCTION</b>	<b>18</b>
1.1 BACKGROUND	18
1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL	18
<b>2 STUDY OBJECTIVES</b>	<b>23</b>
<b>3 STUDY DESIGN</b>	<b>24</b>
3.1 STUDY ENDPOINTS	27
3.2 DEFINITION OF END OF TRIAL	27
<b>4 SELECTION AND ENROLMENT OF PARTICIPANTS</b>	<b>27</b>
4.1 CONSENT	27
4.2 INCLUSION CRITERIA	28
4.3 EXCLUSION CRITERIA	28
4.4 SCREEN FAILURES	29
4.5 REGISTRATION / RANDOMISATION PROCEDURES	29
4.6 CO-ENROLLMENT GUIDELINES	30
4.7 CONTRACEPTION	30
<b>5 TRIAL OBSERVATIONS AND PROCEDURES</b>	<b>31</b>
5.1 SCREENING PROCEDURES	31
5.2 TRIAL PROCEDURES	32
5.3 FOLLOW UP	35
5.4 DEVIATIONS AND SERIOUS BREACHES	36
5.5 DISCONTINUATION OF TRIAL TREATMENT	36
5.6 END OF STUDY AND WITHDRAWAL	37
<b>6 TREATMENTS</b>	<b>37</b>
6.1 TREATMENT SCHEDULE	37
6.2 SUPPORTIVE CARE	40
6.3 DIETARY RESTRICTIONS	40
6.4 IMP SUPPLY	41
6.5 ADMINISTRATION	41
6.6 ADDITIONAL THERAPY FOR DLBCL	43
6.7 ACCOUNTABILITY	43
6.8 PROHIBITED THERAPIES	44
6.9 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY	44
6.10 OTHER ACALABRUTINIB TOXICITY	46

6.11	SAFETY ASSESSMENT	46
6.12	CONCOMITANT MEDICATIONS	46
<b>7</b>	<b>STUDY SAMPLING</b>	<b>47</b>
7.1	PHARMACOKINETIC SAMPLING	47
7.2	PHARMOCODYNAMIC SAMPLING	47
7.3	TRANSLATIONAL RESEARCH	47
<b>8</b>	<b>SAFETY</b>	<b>48</b>
8.1	DEFINITIONS	48
8.2	SERIOUSNESS	49
8.3	CAUSALITY	50
8.4	EXPECTEDNESS	50
8.5	REPORTING PROCEDURES	51
8.6	SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC	53
8.7	SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA	53
<b>9</b>	<b>STATISTICS AND DATA ANALYSES</b>	<b>53</b>
9.1	SAMPLE SIZE	53
9.2	INTERIM ANALYSIS	53
9.3	STATISTICAL ANALYSIS PLAN (SAP)	54
9.4	FINAL ANALYSIS	54
<b>10</b>	<b>REGULATORY</b>	<b>54</b>
10.1	CLINICAL TRIAL AUTHORISATION	54
<b>11</b>	<b>ETHICAL CONSIDERATIONS</b>	<b>54</b>
11.1	SPECIFIC ETHICAL CONSIDERATIONS	54
11.2	ETHICAL APPROVAL	55
11.3	INFORMED CONSENT PROCESS	55
11.4	CONFIDENTIALITY	55
<b>12</b>	<b>SPONSOR</b>	<b>55</b>
12.1	INDEMNITY	55
12.2	FUNDING	55
12.3	AUDITS AND INSPECTIONS	56
<b>13</b>	<b>TRIAL OVERSIGHT GROUPS</b>	<b>56</b>
13.1	TRIAL MANAGEMENT GROUP (TMG)	56
13.2	TRIAL STEERING COMMITTEE (TSC)	56
13.3	SAFETY REVIEW COMMITTEE (SRC)	56
13.4	DATA MONITORING AND ETHICS COMMITTEE (DMEC)	57
<b>14</b>	<b>DATA MANAGEMENT</b>	<b>57</b>
<b>15</b>	<b>MONITORING</b>	<b>58</b>
15.1	CENTRAL MONITORING	58
15.2	CLINICAL SITE MONITORING	58

<b>15.3</b>	<b>SOURCE DATA</b>	<b>59</b>
<b>16</b>	<b>RECORD RETENTION AND ARCHIVING</b>	<b>59</b>
<b>17</b>	<b>PUBLICATION POLICY</b>	<b>59</b>
<b>18</b>	<b>REFERENCES</b>	<b>60</b>
<b>19</b>	<b>APPENDICES</b>	<b>63</b>
<b>20</b>	<b>SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL</b>	<b>76</b>

## LIST OF ABBREVIATIONS

ABC	Activated B-cell
ADCC	Antibody dependent cellular cytotoxicity
ALT	Alanine Aminotransferase
AE	Adverse Event
AR	Adverse Reaction
ARSAC	Administration of Radioactive Substances Advisory committee
AST	Aspartate Aminotransferase
BCR	B-cell Receptor
BSA	Body Surface Area
Btk	Bruton Tyrosine Kinase
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CLL	Chronic lymphocytic Leukaemia
Cmax	Maximum Concentration
CNS	Central Nervous system
COO	Cell of origin
CR	Complete Response
Cru	Complete Response unconfirmed
CRF	Case Report Form
CT	Computer Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic Acid
DLT	Dose Limiting Toxicity
DLBCL	Diffuse Large B-cell lymphoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Group
EGFR	Epidermal Growth Factor Receptor
EMC	Electronic Medicines Compendium
EMA	European Medicine Agency
EORTC	European Organisation for Research and Treatment of Cancer
EFS	Event Free Survival
FBC	Full Blood Count
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescence In Situ Hybridization
FL	Follicular Lymphoma
FNA	Fine Needle Aspirate
GCB	Germinal Centre B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
HBcAB	Hepatitis B core Antibody
HBsAB	Hepatitis B Surface antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HMDS	Haematological Malignancy Diagnostic Service
IB	Investigator's Brochure
IHC	Immunohistochemistry

IMP	Investigational Medicinal Product
IPI	International Prognostic Index
Itk	Interleukine-2-inducible T-cell kinase
IV	Intravenous
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MAD	Maximal administered Dose
MCL	Mantle Cell Lymphoma
MHRA	Medicines and Healthcare products Regulatory Agency
MTD	Maximum Tolerated Dose
NCRI	National Cancer Research Institute
NHL	Non-Hodgkin Lymphoma
Od	Once daily
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear cells
PCP	Pneumocystis jirovecii pneumonia
PK	Pharmacokinetic
PD	Pharmacodynamics
PD	Progressive disease
PET CT	Positron Emission Tomography computer tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PO	By mouth
PR	Partial Response
R	Rituximab
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
RD	Response duration
SAE	Serious Adverse Events
SCTU	Southampton Clinical Trial Unit
SD	Stable Disease
SmPC	Summary of Product Characteristics
SPC	Specific Product Characteristics
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMA	Transcription Mediated Amplification
TMG	Trial Management Group
Tmax	Time to maximum concentration
TTP	Time to Progression
UAR	Unexpected Adverse events
WHO	World Health Organisation
WOCBP	Women of child bearing potential

## KEYWORDS

Diffuse large B-cell lymphoma  
Acalabrutinib  
Btk inhibitor  
R-CHOP  
Molecular profiling  
Chemoimmunotherapy



## TRIAL SYNOPSIS

<b>Short title:</b>	ACCEPT
<b>Full title:</b>	A Phase Ib/II combination trial of acalabrutinib with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP) (for patients with Diffuse Large B-Cell lymphoma)
<b>Phase:</b>	Phase Ib/ II
<b>Population:</b>	Previously untreated CD20 positive diffuse large B-cell lymphoma (DLBCL) requiring full course chemoimmunotherapy.
<b>Primary Objective:</b>	<p><u>Phase I – Dose Escalation</u> To propose a recommended dose for Phase II evaluation of acalabrutinib in combination with R-CHOP in patients with DLBCL:</p> <ul style="list-style-type: none"> <li>- To examine the safety and toxicity profile of acalabrutinib in combination with R-CHOP and defining the dose limiting toxicity or maximum administered dose.</li> </ul> <p><u>Phase II: - Dose Expansion Cohort (as per trial design)</u> To document anti-tumour activity of acalabrutinib in combination with R-CHOP in patients with previously untreated CD20 positive DLBCL</p> <p>To determine additional safety information of acalabrutinib in combination with R-CHOP.</p>
<b>Secondary Objective:</b>	<p>To determine the pharmacokinetic profile of acalabrutinib when given in combination with R-CHOP.</p> <p>To evaluate the effect of acalabrutinib in combination with R-CHOP on outcomes according to cell of origin (COO).</p> <p>To measure the duration of response to acalabrutinib in combination with R-CHOP over a follow-up of 2 years.</p>
<b>Tertiary Objectives:</b>	<p>To determine BTK occupancy by acalabrutinib in peripheral blood mononuclear cells when given in combination with R-CHOP.</p> <p>To determine the impact of the addition acalabrutinib on R-CHOP mediated ADCC</p> <p>To determine evidence of B-cell receptor activation in patients before and after treatment with the combination of R-CHOP and acalabrutinib.</p> <p>To explore the use of tumour-specific circulating DNA in plasma/serum as a non-invasive diagnostic and prognostic tool, with paired lymphoma tissue, through treatment of DLBCL and at follow up.</p> <p>To explore correlation of molecular characteristics in tumour material to clinical outcomes.</p>
<b>Rationale:</b>	Retrospective molecular profiling of untreated DLBCL samples has recognised 3 distinct sub-classifications of this disease (ABC-DLBCL, GCB- DLBCL and unclassified DLBCL), each with unique biological features and clinical outcomes when treated with CHOP or R-CHOP chemotherapy. Dysregulation of B-cell receptors (BCR) signalling pathway is observed in ABC type and requires

	<p>Bruton tyrosine kinase (Btk) activation. Clinical studies have shown that targeting BCR signalling pathway by the inhibition of Btk with ibrutinib (a 1<sup>st</sup> generation Btk inhibitor) in combination with R-CHOP chemotherapy for previously untreated B-cell non-Hodgkin lymphoma is safe. Acalabrutinib is a 2<sup>nd</sup> generation Btk inhibitor with increased target selectivity compared to ibrutinib. It is postulated that the addition of acalabrutinib to R-CHOP chemotherapy may improve tumour response compared to ibrutinib + R-CHOP.</p>
<b>Trial Design:</b>	<p>Open-label non-randomised Phase Ib/II study conducted in two stages. Stage 1 will be dose escalation in a modified classical 6+6 design. Stage 2 will be an expansion cohort to gain additional information on safety and efficacy at the recommended phase II dose of acalabrutinib.</p>
<b>Sample size :</b>	<p>Approximately 40 patients</p>
<b>Investigational Medicinal Product:</b>	<p>Acalabrutinib, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone</p>
<b>Dosage Regimen / Duration of Treatment:</b>	<p>All patients will receive 6 cycles of R-CHOP chemotherapy on a standard 21 days schedule with the addition of acalabrutinib in cycles 2-6. This will be followed by a continuation Phase of acalabrutinib only for 2 cycles of 28 days for each of these 2 cycles</p> <p>Phase I - Dose Escalation</p> <p><b>Stage 1:</b>  <u>R-CHOP + Acalabrutinib (Cycle 2-6)</u></p> <ul style="list-style-type: none"> <li>- Rituximab 375mg/m<sup>2</sup> IV, on day 1</li> <li>- Cyclophosphamide 750mg/m<sup>2</sup> IV, on day 1</li> <li>- Doxorubicin 50mg/m<sup>2</sup> IV, on day 1</li> <li>- Vincristine 1.4mg/m<sup>2</sup> (max 2mg) IV, on day 1</li> <li>- Prednisolone 100mg po, on day1-5</li> <li>- Acalabrutinib, 100mg once daily taken orally, days 1-21</li> </ul> <p><u>Cycle 7 (28 days) and 8 (28 days) - Acalabrutinib only</u></p> <ul style="list-style-type: none"> <li>- Acalabrutinib, 100mg once daily taken orally for 56 days</li> </ul> <p><u>Acalabrutinib dosage:</u>  The first 6 patients enrolled in the study (cohort 1) will receive 100mg od started on day 1 of the 2<sup>nd</sup> cycle of R-CHOP. When patients of the 1<sup>st</sup> cohort have completed their 3<sup>rd</sup> cycle, and their safety data has been reviewed by the safety committee, the decision for dose escalation to 100mg bd for cohort 2 could be taken in accordance with section 6.1.</p> <p><b>Stage 2</b>  <u>R-CHOP + Acalabrutinib (Cycle 2 -6)</u></p> <ul style="list-style-type: none"> <li>- Rituximab 375mg/m<sup>2</sup> IV, on day 1</li> <li>- Cyclophosphamide 750mg/m<sup>2</sup> IV, on day 1</li> <li>- Doxorubicin 50mg/m<sup>2</sup> IV, on day 1</li> <li>- Vincristine 1.4mg/m<sup>2</sup> (max 2mg) IV, on day 1</li> <li>- Prednisolone 100mg po, on day1-5</li> <li>- Acalabrutinib 100mg twice daily, orally days 1-21</li> </ul> <p><u>Cycle 7 (28 days)and 8 (28 days)- Acalabrutinib only</u></p>

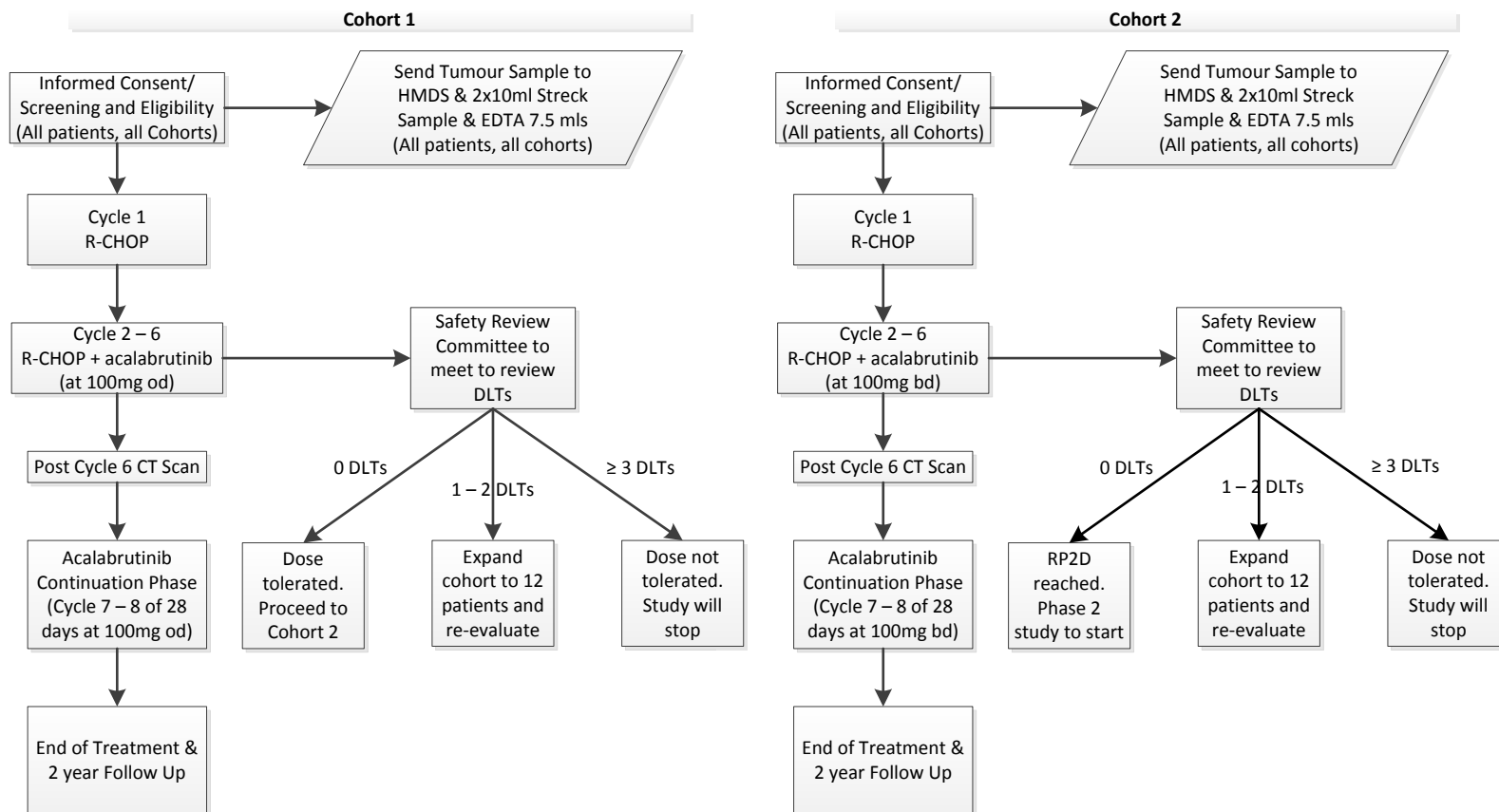
	<ul style="list-style-type: none"> <li>- Acalabrutinib, 100mg twice daily taken orally for 56 days following end of treatment with 6 cycles RCHOP immunochemotherapy.</li> </ul> <p><b>Phase II – Dose Expansion</b></p> <p><u>R-CHOP + Acalabrutinib (Cycle 2 -6)</u></p> <ul style="list-style-type: none"> <li>- Rituximab 375mg/m<sup>2</sup> IV, on day 1</li> <li>- Cyclophosphamide 750mg/m<sup>2</sup> IV, on day 1</li> <li>- Doxorubicin 50mg/m<sup>2</sup> IV, on day 1</li> <li>- Vincristine 1.4mg/m<sup>2</sup> (max 2mg) IV, on day 1</li> <li>- Prednisolone 100mg po, on day 1-5</li> <li>- Acalabrutinib at a Recommended Phase II dose</li> </ul> <p><u>Cycle 7 (28 days) and 8 (28 days) - Acalabrutinib only</u></p> <ul style="list-style-type: none"> <li>- Acalabrutinib, at RP2D taken orally for 56 days following end of treatment with 6 cycles RCHOP immunochemotherapy.</li> </ul>
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<b>URL for Database:</b>	<a href="http://www.imedidata.com/">www.imedidata.com/</a>
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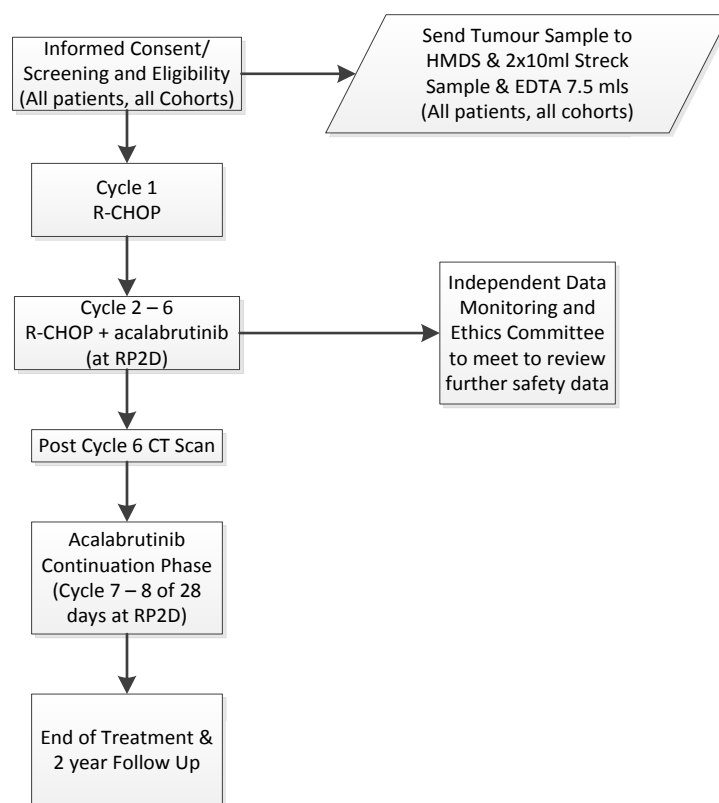
<b>Primary Trial Endpoints:</b>	<p><u>Phase I</u> Dose limiting toxicity of acalabrutinib combined to R-CHOP</p> <p><u>Phase II</u> Overall response rate of the combination acalabrutinib and R-CHOP</p> <p>Safety of the combination acalabrutinib and R-CHOP</p>
<b>Secondary Trial Endpoints:</b>	<p>Pharmacokinetic of acalabrutinib, AUC, C<sub>max</sub>, T<sub>max</sub>, half-life T<sub>1/2</sub> and other PK parameter</p> <p>Overall response rate of the combination acalabrutinib and R-CHOP according to cell of origin.</p> <p>2-years PFS; 2-years overall survival.</p>
<b>Tertiary Trial Endpoints:</b>	<p>Btk occupancy by acalabrutinib on peripheral blood using fluorescent affinity probe assay.</p> <p>Antibody-dependent cell-mediated cytotoxicity of R-CHOP when combined to acalabrutinib, post 1<sup>st</sup> R-CHOP and at day 8, 2<sup>nd</sup> cycle acalabrutinib + R-CHOP.</p> <p>CD86 and CD69 expression as a function of BCR activation by flow cytometry.</p> <p>Tumour-specific DNA in plasma will be sequenced throughout treatment and compared with lymphoma tissue and clinical course.</p> <p>Apply the following techniques to FFPE tumour material: mutational panel, FISH analysis, immunohistochemical analysis for dual protein expression of Myc and Bcl2 and gene expression profiling using whole transcriptome profiling.</p>
<b>Total Number of Sites :</b>	7 UK sites

## TRIAL SCHEMA

### PHASE Ib – DOSE ESCALATION



## PHASE II – DOSE EXPANSION



## SCHEDULE OF OBSERVATIONS AND PROCEDURES

### REGISTRATION AND CYCLE 1

Visit	Screening <sup>a</sup>						Cycle 1
Weeks							1
Days	Within 90 days of treatment	Within 35 days of treatment	Within 28 days of treatment	Within 14 days of treatment	Within 72 hours of treatment	Prior to treatment	R-CHOP
Informed consent			X				
Inclusion/ Exclusion criteria				X			
Medical History				X			
Physical Exam				X			
IPI and NCCN-IPI*				X			
Vital signs <sup>b</sup>				X			X
ECOG performance Status				X			X
PET-CT or contrast enhanced CT with separate PET <sup>c</sup>		X					
Bone marrow biopsy <sup>d</sup>	X						
Biochemistry: renal and liver function <sup>e</sup>				X			
Biochemistry: Additional baseline panel <sup>f</sup>					X		
Haematology <sup>g</sup>					X		
Immunoglobulins					X		
Hepatitis B, C and HIV serology <sup>h</sup>			X				
Pregnancy test <sup>i</sup>						X	
Electrocardiogram <sup>j</sup>			X				
Echocardiogram/MUGA <sup>k</sup>			X				
Cerebrospinal fluid examination <sup>l</sup> (if clinically indicated)			X				
Tumour material <sup>m</sup>			X				
Streck Plasma DNA Sample <sup>n</sup>			X				
EDTA Sample <sup>n</sup>						X	
Concomitant Medications				X			X
Adverse Events <sup>o</sup>			X	X	X	X	X
R-CHOP							X

<sup>a</sup> Screening investigations to be performed within 14 days of starting study medication with the exception of informed consent, CT, Electrocardiogram and Bone marrow biopsy

<sup>b</sup> Blood pressure, pulse, temperature, height and weight. Assessment to be performed pre-dose and as per local practice during rituximab infusion

<sup>c</sup> PET and Contrast Enhanced CT of chest, abdomen and pelvis (neck if indicated) should be carried out within 35 days of planned treatment. The PET-CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality and includes the use of intravenous (IV) contrast. If this cannot be achieved, a PET and separate Contrast Enhanced CT scan should be performed. Bi-dimensional measurements are expected.

<sup>d</sup> Bone marrow aspirate and trephine biopsy (single site with adequate trephine) (within 90 days of first treatment).

<sup>e</sup> Serum chemistry to include sodium, potassium, urea, creatinine, bilirubin, alanine or aspartate transaminase, alkaline phosphatase and albumin.

<sup>f</sup> Additional serum chemistry to be performed only at baseline: LDH, calcium, phosphate,  $\beta$ 2-microglobulin and uric acid.

<sup>g</sup> Full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelets counts. To be taken within 72 hours of chemotherapy administration on each cycle

<sup>h</sup> As per standard of care, sites should have hepatitis results available prior to initiation of immunochemotherapy.

<sup>i</sup> Only required in females of child bearing potential on day 1 before treatment commences

<sup>j</sup> A 12 lead ECG should be performed on all patients.

<sup>k</sup> In addition, an Echocardiogram or MUGA will be performed for all patients to establish a left ventricular ejection fraction equal to or greater than institutional normal range. Patients should be considered suitable to receive 300mg/m<sup>2</sup> doxorubicin

<sup>l</sup> Cerebrospinal fluid examination should be performed if clinically indicated or lymphomatous involvement of peripheral blood, nasal/paranasal sinuses or testis. CNS prophylaxis may be given according to local policy

<sup>m</sup> Diagnostic tumour block to be forwarded immediately upon obtaining either Tissue Block Screening consent or main study consent (for those patients whose tissue sample is easily accessible) to HMDS, Leeds, according to study procedure outlined in Investigator Site File.

<sup>n</sup> 20ml Blood sample in 2x10ml Streck tubes and 1x7.5ml EDTA Blood sample to be forwarded immediately to HMDS, Leeds prior to treatment start.

<sup>o</sup> Adverse Events to be collected from date of consent. Only Adverse Events related to study procedures should be reported prior to start of treatment.

\*Please see Appendix 3

## CYCLES 2 – END OF TREATMENT

Visit:	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day1	Cycle 4 Day 8	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 <sup>x</sup>	Cycle 8 <sup>x</sup>	End of Treatment <sup>bb</sup>
Weeks:	4	5	6	7	10	11	13	16	19 <sup>w</sup>	23	27-30
Physical Exam <sup>y</sup>	X			X	X		X	X	X	X	X
Vital Signs <sup>p</sup>	X	X	X	X	X	X	X	X	X	X	X
ECOG performance Status <sup>y</sup>	X	X	X	X	X	X	X	X	X	X	X
Contrast enhanced CT									X <sup>aa</sup>		
PET-CT or contrast enhanced CT and separate PET <sup>q</sup>											X <sup>q</sup>
Bone marrow biopsy <sup>r</sup>											(X) <sup>r</sup>
Biochemistry: renal and liver function <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X
Haematology <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram <sup>z</sup>				X			X		X		X
Echocardiogram <sup>z</sup>					X						X
Pharmacokinetic samples <sup>cc</sup>	X	X	X	X							
Pharmacodynamic samples <sup>cc</sup>	X	X			X						
R-CHOP + acalabrutinib	X			X	X		X	X			
Acalabrutinib (only) <sup>x</sup>									X	X	
Compliance <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Streck Plasma DNA Sample <sup>v</sup>	X			X							X
Immunoglobulins				X							X
Pregnancy Test	X			X	X		X	X	X	X	X

<sup>p</sup> Blood pressure, pulse and temperature. Assessment to be performed pre-dose and as per local practice during rituximab infusion

<sup>q</sup> PET and Contrast Enhanced CT of chest, abdomen and pelvis (neck if indicated) needs to be completed within 3 weeks of the patient completing last treatment cycle. The PET-CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality and includes the use of intravenous (IV) contrast. If this cannot be achieved, a PET and separate Contrast Enhanced CT scan should be performed. Bi-dimensional measurements are expected.

<sup>r</sup> Bone marrow biopsy to be repeated at the end of treatment if initially involved (to confirm CR)

<sup>s</sup> Serum chemistry to include sodium, potassium, urea, creatinine, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, LDH and albumin. To be taken within 72 hours of administration of each cycle

<sup>t</sup> Full blood count including haemoglobin, white cell count, absolute neutrophil count, lymphocytes and platelets. To be taken within 72 hours of chemotherapy administration on each cycle

<sup>u</sup> Compliance will be assessed by patient's diary with date and time of acalabrutinib administration, and the count of remaining capsules



<sup>v</sup> 20ml Blood sample in 2x10ml Streck tubes to be forwarded immediately to HMDS, Leeds

<sup>w</sup> End of RCHOP + acalabrutinib treatment at week 19 is also the start of the continuation phase of acalabrutinib. The dosing of acalabrutinib is continued after the last day of treatment (cycle 6 day 21) for 56 days further.

<sup>x</sup> Acalabrutinib only is given for cycles 7 and 8 as a continuation phase on a 28 days per cycle schedule - a total of 56 days continuation phase.

<sup>y</sup> Physical exam and ECOG performance status. To be taken within 48 hours of acalabrutinib administration.

<sup>z</sup> Electrocardiogram and Echocardiogram to be taken within 48 hours of acalabrutinib administration.

<sup>aa</sup> CT scan to be completed during Week 19 (+/- 1 week)

<sup>bb</sup> EoT visit should take place within 3 weeks from the final dose of acalabrutinib.

<sup>cc</sup> Post dose samples should be taken at the protocol specified time  $\pm$  5 minutes.

## SCHEDULE OF FOLLOW-UP VISITS

Follow up visits begin 3 months following cycle 8 (at the end of the acalabrutinib continuation phase- at week 39).

Months following last therapy <sup>gg</sup>	3	6	9	12	16	20	24
Physical Exam	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X	X
Biochemistry <sup>dd</sup>	X	X	X	X	X	X	X
CT <sup>ee</sup>				X			X
Adverse Events	X	X	X	X	X	X	X
Streck Plasma DNA Sample <sup>ff</sup>	X	X	X	X	X	X	X
Immunoglobulins		X		X			X
Pregnancy Test	X	X	X	X			

<sup>dd</sup> Serum chemistry to include sodium, potassium, urea, creatinine, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, LDH and albumin.

<sup>ee</sup> A contrast enhanced CT scan of the neck, chest, abdomen and pelvis will be performed at 12 months and 24 months following completion of protocol specified therapy. Bi-dimensional measurements are expected.

<sup>ff</sup> 20 ml Blood sample in 2x10ml Streck tubes to be forwarded immediately to HMDS, Leeds.

<sup>gg</sup> A visit window of +/- 2 weeks is permitted for follow-up visits.

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

# 1 INTRODUCTION

## 1.1 BACKGROUND

More than 10,000 new cases of non-Hodgkin's lymphoma (NHL) are diagnosed in the UK with approximately 4,500 attributable deaths each year (Cancer Research UK accessed August 2009) <sup>1</sup>. In the Western World, diffuse large B-cell lymphoma (DLBCL) comprises one third of all adult NHL cases (The Non-Hodgkin's Lymphoma Classification Project 1997) <sup>2</sup>, accounting for an annual incidence in the UK of approximately 3,000 patients.

For many years CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) was the standard of care for DLBCL although overall survival was disappointing, with only about half the patients cured (Fisher, *et al* 1993) <sup>3</sup>. The concurrent use of the anti CD20 monoclonal antibody rituximab resulted in a major paradigm shift with higher response rates, longer event free survival and improved overall survival, so that R-CHOP is now accepted as the international standard, with cure rates around 75% (Coiffier, *et al* 2002) <sup>4</sup>, (Habermann, *et al* 2006) <sup>5</sup>, (Pfreundschuh, *et al* 2008) <sup>6</sup>, (Pfreundschuh, *et al* 2006) <sup>7</sup>, (Sehn, *et al* 2005) <sup>8</sup>.

Despite this improvement, a substantial number of patients still have disease which either fails to respond to initial therapy, or relapses after initial remission. The majority of these will die as a result of their disease, because the success of salvage treatment appears to be limited after prior rituximab treatment (Gisselbrecht, *et al* 2009) <sup>9</sup>. There is therefore a need to further improve the efficacy of first line treatment.

One approach has been to increase the dose density of CHOP, giving it every 14 days with growth factor support instead of every 21 days. The German NHL-B2 trial conducted in elderly patients with DLBCL, but not using rituximab, found that this approach was superior with a 5 years event free survival of 44% in the CHOP-14 arm and 33% in the CHOP-21 arm (Pfreundschuh, *et al* 2004a) <sup>10</sup>, although no such benefit could be identified in younger patients studied in the companion NHL-B1 study (Pfreundschuh, *et al* 2004b) <sup>11</sup>. The benefit of adding rituximab to the R-CHOP 14 schedule was demonstrated in the RICOVER-60 trial (Pfreundschuh, *et al* 2008) <sup>6</sup>. This also demonstrated that there was no benefit of 8 cycles over 6 cycles of immunochemotherapy. The UK NCRI study of R-CHOP 14 vs 21 included 1080 patients of all ages and closed to recruitment in November 2008 (Cunningham, *et al* 2009) <sup>12</sup>. Preliminary results have been reported which indicate that the more intensive schedule is not associated with an improvement in the complete response rate, and there have not yet been sufficient events for an analysis of its primary endpoint of PFSI. Results from a planned interim analysis of the GELA LNH03-6B study of R-CHOP 14 against R-CHOP 21 in older patients have recently been reported (Delarue, *et al* 2009) <sup>13</sup>. These demonstrate no significant difference in event free survival at 2 years (48% and 61% respectively).

An alternative approach is to consider adding more agents. One of the options is to add more conventional cytotoxics, but this has not proven to improve upon CHOP in randomised studies (Fisher, *et al* 1993) <sup>3</sup>. With increased knowledge of the biology of DLBCL and the availability of new targeted therapeutics based upon the pathogenetic abnormalities in the lymphoma cells, the other option is the addition of targeted therapeutics to classical immunochemotherapy.

## 1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Understanding the molecular biology of DLBCL is the cornerstone of the new strategies to improve DLBCL outcomes. Gene expression profiling has provided new insights into the biology of DLBCL by identifying three distinct phenotypes of DLBCL, germinal centre B-cell like (GCB), activated B-cell like (ABC) and unclassifiable DLBCL, with different oncogenic mechanisms and distinct clinical outcomes. ABC type is characterized by constitutive activation of the nuclear factor-KB (NF-KB) signalling pathway leading to inhibition of apoptosis. The inhibition of NF-KB pathway with bortezomib is one of the

targeted therapies in DLBCL being under investigation in REMoDL-B study conducted by the UK National Cancer Research Institute, in association with the Swiss SAKK Group <sup>14</sup>.

B-cell receptor (BCR) is one of the main signalling pathways of B-cell. BCR is a transmembrane immunoglobulin (Ig) receptor associated with Ig-alpha (CD79a) and Ig-beta (CD79b) heterodimers. BCR serves as an antigen receptor and regulates multiple cellular processes, including proliferation, differentiation, apoptosis and cell migration (Navaro et al 2014) <sup>15</sup>. Bruton tyrosine kinase (Btk) is a non-receptor cytoplasmic kinase which is expressed in almost all haematopoietic cells, except T-cells and plasma cells. Btk is one the five members of the Tec family kinase (Btk, Tec, Itk, Txk, Bmx) (Mohamed et al 2009) <sup>16</sup>, (Bradshaw et al 2010) <sup>17</sup>. The Btk gene is located on X-chromosome at Xq21.33-Xq22. Functional null mutation of Btk gene in humans causes inherited disease, X-linked agammaglobulinemia, which is characterised by a lack of mature peripheral B cells (Vihinen et al 2000) <sup>18</sup>. Btk and phosphatidylinositol 3-kinase (PI3-k), another cytoplasmic kinase, are both essential for BCR signalling pathway. The activation of Btk and PI3-k after antigen binding to BCR results in stimulation of transcription factors, mainly NF-KB, leading to inhibition of apoptosis and therefore cell proliferation and survival of B-cells. It has been demonstrated that several B-cell malignancies exhibit activation of BCR signaling pathway and especially through Btk activation (Buggy et al 2012) <sup>19</sup>. Taken together, these findings have suggested that inhibition of Btk may offer an attractive strategy for treating B-cell malignancies which has led to the development of Btk inhibitors. Ibrutinib is the first generation orally active irreversible small molecule Btk inhibitor through bonding with cysteine-481 in the active site of BTK. Ibrutinib has been tested in relapse/refractory mantle cell lymphoma with an ORR of 68% (21% CR and 47% PR) (Wang et al 2013) <sup>20</sup>. In a Phase Ib/II study, ibrutinib was tested in 85 patients with relapse/refractory chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) with an ORR of 71%, a 26-month PFS of 75% and OS of 83% (Byrd, NEJM) <sup>21</sup>. This has allowed ibrutinib to be approved for chronic lymphocytic leukemia and mantle cell lymphoma by the EMEA in July 2014.

It has been demonstrated that tumour cells of ABC type DLBCL are driven by “chronic active” BCR signalling (Davis et al 2010)<sup>22</sup>. The inhibition of BCR signalling pathway using first generation Btk inhibitor, ibrutinib has proven efficacy in ABC type DLBCL. A phase II study (Wilson et al, 2012) <sup>23</sup> was conducted in relapsed/refractory DLBCL, where seventy patients received single agent, ibrutinib. Overall response rate was 40% (8% CR, 32% PR) in ABC type subgroup (n=29) versus 5.3% (0 CR, 5.3% PR) in GCB subgroup (n=20), suggesting better outcomes in ABC type. In previously untreated CD20 positive B-cell non-Hodgkin lymphoma, ibrutinib has been combined with conventional R-CHOP in a phase Ib/II dose-escalating study (Younes et al, 2013) <sup>24</sup>, demonstrating its safety combined with R-CHOP (maximum dose tolerated not reached). Overall response rate in all DLBCL patients was 91% with (70% CR) and 100% in patients who received the recommended phase II dose of ibrutinib. There was no difference in outcomes according to cell of origin, but numbers were small.

While highly potent in inhibiting Btk, ibrutinib has also shown in vitro activity against other kinases to which the drug covalently binds. In addition, ibrutinib is primarily metabolised by CYP3A. Thus, ibrutinib dosing must be halted or reduced when co-administered with drugs that are strong or moderate inhibitors of CYP3A (Ibrutinib prescribing information). Acalabrutinib is a second generation orally active molecule which covalently inhibits Btk and was designed to be a more potent and selective inhibitor of Btk to avoid off-target side effects as seen with ibrutinib. Both ibrutinib and acalabrutinib are covalent inhibitors of Btk, by forming a covalent interaction with Cysteine 481 in the front position of the ATP-binding pocket of Btk. There are 9 more kinases (group of 3F-Cyst) with a cysteine in the same position than Btk: Tec, Bmx, Itk, Txk, EGFR, ErbB2, ErbB4, Blk and JAK3 (Barf and Kaptein, 2012) <sup>25</sup>. Potency of acalabrutinib and ibrutinib on Group 3F-Cyst Kinases has been compared. Ibrutinib showed strong inhibition of all Group 3F-Cyst Kinases, while for acalabrutinib, the strongest inhibition was observed for Btk, with inhibition as well of Tec, Bmx and ErbB4, but no inhibition of Itk, EGFR, Blk, ErbB2 and JAK3.

The inhibition of epidermal growth factor receptor (EGFR) by ibrutinib is also observed in cellular assays and may be the cause of ibrutinib-related adverse events of diarrhoea, rash and haemorrhage. Acalabrutinib has minimal effect on EGFR, which may postulate less gastro-intestinal, cutaneous and

haemorrhagic adverse events. The effects of acalabrutinib and ibrutinib on thrombus formation were evaluated on human platelet-mediated thrombosis by using the in vivo human thrombus formation in a VWF murine model. Purified human platelets were pre-incubated with various concentrations of ibrutinib and acalabrutinib or DMSO and then administered to VWF mice followed by laser-induced thrombus formation. Ibrutinib and acalabrutinib-treated human platelets were fluorescently labelled and infused continuously through a catheter inserted into the femoral artery. Thrombus formation in response to laser-induced vascular injury was monitored in real time using 2-channel confocal intravital microscopy. Upon arteriole injury untreated platelets rapidly formed thrombi with a mean thrombus size of  $6,450 \pm 292 \text{ mm}^2$ . Similarly, acalabrutinib treated platelets formed slightly smaller but not significantly different thrombi, with a mean thrombus size of  $5733 \pm 393 \text{ mm}^2$ . In contrast, a significant reduction in thrombus size occurred in platelets pre-treated with ibrutinib, mean size was  $2600 \pm 246 \text{ mm}^2$ , representing a reduction in maximum size of approximately 61% compared with control. These preliminary results may explain grade  $\geq 3$  bleeding adverse events reported in  $\leq 6\%$  of patients treated with ibrutinib. Additionally, they may be the basis to postulate less risk of bleeding with acalabrutinib.

Itk is a kinase required for FcR-stimulated NK cell function including calcium mobilization, granule release and overall antibody-dependent cell-mediated cytotoxicity (ADCC). Ibrutinib strongly inhibit Itk and has been recently reported to interfere with ADCC activity of CD20 antibodies (Da Roit et al, 2014)<sup>26</sup>. Acalabrutinib which does not have activity against Itk may preserve NK cell function and therefore synergize rather than antagonize anti-CD 20 mediated ADCC.

Administration of acalabrutinib with a high fat, high calorie meal did not have a clinically significant effect on exposure, so acalabrutinib can be taken without regard to meals. In healthy volunteer studies, agents that lowered gastric acidity (e.g., calcium carbonate and omeprazole) lowered exposure of concomitantly administered acalabrutinib. Acalabrutinib is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition of cytochrome P450 (CYP) isoforms. However, the mean plasma acalabrutinib maximum concentration ( $C_{\max}$ ) and area under the curve (AUC) values increased 3.7 – and 5.1-fold respectively, in the presence of itraconazole, a strong CYP3A inhibitor, relative to no pre-treatment. Rifampin, a strong CYP3A inducer, dosed at 600mg once daily (QD) for 9 days, decreased AUC to 23% of values obtained with acalabrutinib dosed alone. Based on available pre-clinical and clinical data, acalabrutinib is cleared by multiple CYP and non-CYP metabolic pathways. CYP-3A-mediated oxidation appears to be a major route of metabolism in humans (See Investigator's Brochure for more information).

Acalabrutinib is not a potent direct inhibitor of CYP3A4 and is not anticipated to be a perpetrator of drug interactions at the level of systemic inhibition of CYP3A4 ( $[I]_1/IC_{50}$  ratio=0.03). A 100mg dose of acalabrutinib may increase exposure to co-administered CYP3A substrates by transient inhibition of intestinal CYP3A ( $[I]_2/IC_{50}$ =15.1). A SimCYP<sup>TM</sup> population-based absorption, distribution, metabolism and elimination (ADME) simulator physiologically based pharmacokinetic (PBPK) model for acalabrutinib indicated no change in exposure to orally co-administered midazolam (a sensitive CYP3A substrate) in the presence of acalabrutinib.

Acalabrutinib co-administration may increase exposure to BCRP substrates by inhibition of intestinal BCRP. Acalabrutinib is not anticipated to alter PK of other therapeutic agents that are substrates for P-gp, OATPB1, OATPB3, OAT1, OAT3 and OCT2.

Acalabrutinib biological activity has been demonstrated in a spontaneous large animal model of human NHL. Acalabrutinib has been evaluated in an ongoing study in canine spontaneous B-cell lymphoma. In a canine lymphoma model, fourteen dogs, all of which had DLBCL confirmed by histology, have been treated with acalabrutinib for at least 2 weeks. The dosages ranged from 2.5 to 20 mg/kg daily or twice daily. To date, per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma, partial responses have been observed in 4 of 14 dogs (29%) and stable disease in 8 of 14 dogs (57%). No acalabrutinib AEs have been reported to date in this study. These findings are similar to the clinical responses observed with ibrutinib in dogs with spontaneous B-cell

lymphoma. Currently >20 human studies are ongoing or about to open in a range of B-cell malignancies examining the activity of acalabrutinib. ACE-CL-001 (NCT02029443)<sup>27</sup>, an ongoing Phase I/II study in patients with relapsed/refractory or previously untreated CLL, Richter's syndrome, or prolymphocytic leukaemia has a sequential, dose-escalating design. As of 01 October 2015, 60 patients with relapsed CLL have been evaluated for tumour response based on International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include PR with treatment-induced lymphocytosis. With a median follow-up of 14.3 months, on ORR of 95% has been observed (Byrd 2015).

Acalabrutinib has been administered at dosages from 100 to 400 mg QD or 100 to 200 mg BID for up to 14 cycles (1 cycle = 28 days). Patients have received acalabrutinib at dosages from 100 to 400 mg od or 100 to 200 mg bd. Pharmacokinetic results showed exposure to acalabrutinib was generally dose proportional with no drug accumulation. On Day 8, mean peak plasma values occurred between 0.64 and 1.1 hours. Mean half-life was approximately 1 hour across all dose cohorts. Acalabrutinib has been well tolerated at all dose levels evaluated. No DLTs have occurred at any dose level. The MTD was not reached in this study, and the dose escalation was stopped at 400 mg.

As of 30 December 2018, acalabrutinib has been administered to over 2600 participants in clinical studies, including patients with haematologic malignancies, solid tumour, or rheumatoid arthritis, and participants who are healthy volunteers or with mild to moderate hepatic impairment. No SAEs have been reported in the hepatic impairment study or in the healthy volunteer studies. No expected serious adverse reactions have been identified for acalabrutinib to date. For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator's Brochure.

The preclinical and clinical observations presented above make a compelling case for the clinical investigation of R-CHOP in combination with acalabrutinib for the treatment of patients with DLBCL. The efficacy and safety of ibrutinib in combination with R-CHOP has already been investigated in Phase Ib/II, demonstrating that it is well tolerated with an ORR of 91% (CR 70%). This argues that no extensive preclinical modelling is required for acalabrutinib + R-CHOP.

### **Summary: Rationale for combination of acalabrutinib in combination with R-CHOP in DLBCL**

The preclinical and clinical observations presented above make a compelling case for the clinical investigation of R-CHOP in combination with acalabrutinib for the treatment of patients with DLBCL.

Despite the success of R-CHOP chemotherapy in DLBCL, many patients will either fail to respond or relapse after completion of therapy. The outcomes for these groups of patients are poor and new therapeutic options are therefore required.

Dysregulation of BCR signalling is well recognised in DLBCL and other B-cell malignancies. BTK is central to signalling through the BCR. A proof of principle study in DLBCL has already been conducted demonstrating that single agent therapy the first generation BTK inhibitor, ibrutinib, in relapsed and refractory DLBCL has meaningful clinical activity with preferential benefit in tumours of the ABC subtype with an ORR of 40% [16].

The second generation BTK inhibitor, acalabrutinib has a number of preclinical properties that would indicate the potential for favourable efficacy and safety over ibrutinib. These include preferential selectivity for BTK with the potential for less off-target effects (e.g. EGFR and diarrhoea). Acalabrutinib does not appear to abrogate thrombus formation, compared to ibrutinib, mediated by off-target kinase activity, and would therefore potentially reduce the risk of bleeding and also compared to ibrutinib does not have a negative effect on ADCC, an important mediator of rituximab function.

Acalabrutinib has preclinical activity in DLBCL xenograft and canine models and is already demonstrating considerable clinical activity in CLL.

Data presented demonstrates a low potential for drug-drug interaction with acalabrutinib as it is neither a strong direct inhibitor or inducer of cytochrome P450 (CYP) isoforms. This is advantageous given the considerable number of concomitant medications prescribed to patients undergoing therapy for DLBCL.

Results from the study of acalabrutinib in patients with CLL demonstrate a favourable toxicity profile with an emergent lower rate of haematological toxicity compared to ibrutinib. No DLTs were reached and no SAEs reported to date at doses  $\leq 400$ mg.

The safety and efficacy of ibrutinib in combination with R-CHOP has already been investigated by a Phase Ib study in patients with DLBCL, demonstrating that it is well tolerated with an ORR of 91% (CR 70%) [14]. Numbers were small, but there was no difference in outcomes according to classification by the ABC or GCB criteria. This argues that no extensive preclinical modelling is required for the acalabrutinib + R-CHOP.

In the dose escalation phase of ACCEPT, 12 patients were treated. The combination was well tolerated and no new safety concerns were observed at the maximally treated dose of acalabrutinib 100mg bd. Recruitment to the dose expansion phase continues with 12 of a planned 15 patients treated. Again, there has been no new safety signal and efficacy data will be reported when recruitment has been completed.

In the randomised Phase III PHOENIX study (n=838 patients) (NCT01855750) reported Younes et al <sup>32</sup>, the American Society of Haematology Meeting in December 2018, the addition of ibrutinib to R-CHOP (IR-CHOP) was compared to R-CHOP alone in patients with *de novo* DLBCL of the non-GC phenotype (defined by central laboratory immunohistochemistry). The addition of the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib (I) to R-CHOP (R-CHOP-I) did not improve the outcome of the study population although R-CHOP-I treated patients aged less than 60 years had a significantly improved progression free survival (PFS) and overall survival (OS) compared to those receiving R-CHOP. In patients aged over 60 years, the addition of I increased toxicity and compromised the delivery of R-CHOP. Acalabrutinib (A) is a second generation BTKi, with enhanced kinase selectivity and potential for better efficacy and tolerability over first-generation inhibitors. Analysis of early safety data from ACCEPT demonstrates no safety concerns or compromise of delivery of full course R-CHOP when combined with acalabrutinib.

### **Rationale for dose selection**

Results from the study of ibrutinib in combination with R-CHOP indicate that the maximal tolerated dose was not reached [17] and the recommended Phase II dose of ibrutinib was 560mg od. This is licensed single agent dose for use in mantle cell lymphoma. Given the favourable single agent toxicity profile of acalabrutinib in the CLL study compared to ibrutinib, it is anticipated that acalabrutinib may safely be given in combination with R-CHOP at doses close or equivalent to those being investigated as a single agent.

Preliminary data from the ongoing Phase I/II study in patients with relapsed/refractory or previously untreated CLL have shown that acalabrutinib is well tolerated at dosages of 100 to 400 mg od and 100 to 200 mg bd. These data suggest that *de novo* synthesis of BTK can occur within 24 hours in peripheral blood cells. Twice daily dosing may ensure BTK inhibition for the entire 24 hours and thus may be beneficial in terms of increasing efficacy and/or decreasing development of resistance to acalabrutinib.

Taken together, the proposed starting dose of 100mg od is considered represent one where there is good pharmacodynamic evidence that the target is being suitably occupied without safety concerns in single agent studies and one supported by our pharmacokinetic knowledge of acalabrutinib. Escalation to twice daily dosing in the second cohort, addresses the continued inhibition of BTK based upon concerns about *de novo* synthesis during the 24-hour period.

## 2 STUDY OBJECTIVES

	Objective	Endpoint used to evaluate
<b>Primary:</b>	<u>Phase I – Dose Escalation</u>	<u>Phase I</u>
	To propose a recommended dose for Phase II evaluation of acalabrutinib in combination with R-CHOP in patients with DLBCL:	Dose limiting toxicity of acalabrutinib combined to R-CHOP.
	- To examine the safety and toxicity profile of acalabrutinib in combination with R-CHOP and defining the dose limiting toxicity or maximum administered dose.	
	<u>Phase II: - Dose Expansion</u>	<u>Phase II</u>
	To document anti-tumour activity of acalabrutinib in combination with R-CHOP in patients with previously untreated CD20 positive DLBCL	Overall response rate of the combination acalabrutinib and R-CHOP.
	To determine additional safety information of acalabrutinib in combination with R-CHOP.	Safety of the combination acalabrutinib and R-CHOP.
<b>Secondary:</b>	To determine the pharmacokinetic (PK) profile of acalabrutinib when given in combination with R-CHOP in patients with DLBCL.	Pharmacokinetic of acalabrutinib, AUC, Cmax, Tmax, half-life $T_{1/2}$ and other PK parameter.
	To evaluate the effect of acalabrutinib in combination with R-CHOP on outcomes according to COO	Overall response rate of the combination acalabrutinib and R-CHOP according to COO
	To measure the duration of response to acalabrutinib in combination with R-CHOP over a follow-up period of 2 years	2-years progression-free survival; 2-years overall survival.
<b>Tertiary:</b>	To determine BTK occupancy by acalabrutinib in peripheral blood mononuclear cells when given with R-CHOP.	Btk occupancy by acalabrutinib on peripheral blood using fluorescent affinity probe assay.

To determine the impact of addition of acalabrutinib on R-CHOP mediated ADCC.	Antibody-dependent cell-mediated cytotoxicity of R-CHOP when combined to acalabrutinib, post 1st R-CHOP and at day 8, 2nd cycle acalabrutinib + R-CHOP.
To determine evidence of B-cell receptor (BCR) activation in patients before and after treatment with combination of R-CHOP and acalabrutinib.	CD86 and CD69 expression as a function of BCR activation by flow cytometry.
To explore the use of tumour-specific circulating DNA in plasma/serum as a non-invasive diagnostic and prognostic tool, with paired lymphoma tissue, through treatment of DLBCL and at follow up.	Tumour-specific DNA in plasma will be sequenced throughout treatment and compared with lymphoma tissue and clinical course.
To explore correlation of molecular characteristics in tumour material to clinical outcomes.	Apply the following techniques to FFPE tumour material: mutational panel, FISH analysis, immunohistochemical analysis for dual protein expression of Myc and Bcl2 and gene expression profiling using whole transcriptome profiling.

### 3 STUDY DESIGN

A multicentre open-label non-randomised phase Ib/II clinical trial conducted in two stages recruiting approximately 40 patients. Stage 1 will be dose escalation following the conventional rules of 6+6 modified design, escalation will proceed until a maximum tolerated dose (MTD) is defined or the maximal administered dose (MAD) is determined in order to define the recommended Phase II dose (RP2D). A 6 patients cohort design is employed to maximise patient safety<sup>30</sup>, which will result in 6 - 24 patients recruited. Stage 2 will be an expansion cohort in order to gain additional information on safety and efficacy at the RP2D from a total of 15 patients recruited.

Patients will receive conventionally dosed R-CHOP chemotherapy for 6 cycles with acalabrutinib introduced on cycle 2 onwards, at a dosage according to cohort number. This will allow for both clarity in the toxicity profile of the combination and assess the impact of acalabrutinib on ADCC.

For both stages, patients who do not complete six cycles of treatment for reasons other than toxicity will be replaced.

#### Phase I: Dose escalation

##### *Cohort 1:*

Following informed consent, the first 6 patients registered (cohort 1) will receive a first cycle of R-CHOP. Acalabrutinib, at a starting dose of 100 mg od, will be added from cycle 2 to 6. This will be followed by cycles 7 and 8 of acalabrutinib only 100mg od for 28 days for each cycle. To ensure compliance patients will receive a diary to record a specific time each dose was taken and record reasons for missed doses. Patients will be instructed to bring the diary and any remaining capsules to clinic at their next visit where subject compliance will be assessed.



Dose escalation to 200 mg daily (100 mg bd) of acalabrutinib will be decided by the Safety Review Committee based on safety data and patients' compliance assessment. PK/PD measurements, if available, will be taken into account at the time of safety review, but this will not be rate limiting for the decision to dose escalate, especially if the combination is well tolerated based on the toxicity profile, after all patients of cohort 1 have completed their 2<sup>nd</sup> cycle of acalabrutinib + R-CHOP (3<sup>rd</sup> cycle of therapy). If one to two instances of DLT (DLT explained below) is observed among six patients, the cohort will be expanded to a further six patients.

If a DLT attributable to acalabrutinib occurs, acalabrutinib will be withheld and R-CHOP continued. If no further DLTs occur within the 12 patients, dose escalation will occur (please see **Table 1**) upon review by the Safety Review Committee (as defined in section 13.3).

#### *Cohort 2:*

The first 6 patients of cohort 2 will start acalabrutinib + R-CHOP at the daily dose of 200mg administered as 100mg bd from cycle 2 after the Safety Review Committee has approved dose escalation based on all the safety data from cohort 1. After all patients of cohort 2 have completed their 2<sup>nd</sup> cycle of acalabrutinib + R-CHOP (3<sup>rd</sup> cycle of therapy), and based on patients' safety data, compliance assessment, PK/PD measures if available, the Safety Review Committee will assess the safety of 200mg. If one or two instances of DLT is observed among the initial six patients of cohort 2, the cohort will be expanded to a further six patients. Depending on tolerability as set out, cohort 2 patients should receive cycle 1 of R-CHOP, cycles 2-6 R-CHOP plus acalabrutinib and then cycles 7 and 8 of acalabrutinib only at 200mg administered as 100mg bd.

If a DLT attributable to acalabrutinib occurs, acalabrutinib will be withheld for that patient and reintroduced at 100 mg od when toxicity has resolved to < grade 1, all other patients will continue at acalabrutinib dosage of 200mg. If  $\geq 3$  DLTs are attributable to acalabrutinib in the initial six patients acalabrutinib will be withheld from the patient(s) who have suffered the DLT and reintroduced at 100 mg od after toxicity has resolved to < grade 1 and all other patients' dosage will be decreased to 100 mg od.

When all patients have completed all 6 cycles of therapy, the Safety Review Committee will review patients' compliance assessment, PK/PD measurements if available and safety data, including the identified MTD and MAD, to determine the recommended dose for Phase II (RP2D) which will be a dose where  $\leq 33\%$  of patients had a DLT.

#### Definition of DLT:

The dose limiting toxicity (DLT) will be defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse events (CTCAE) version 4.03. The maximum tolerated dose (MTD) is defined as the highest dose level at which none of the first six treated patients, or no more than 2 of the first 12 treated patients, experiences a DLT.

The DLT reporting period is from the start of treatment until the end of cycle 3. Events meeting the below criteria following the end of cycle 3 will not be recorded as DLTs.

A DLT will be defined as the occurrence of the following:

- Grade 2 or greater haemorrhagic event requiring medical intervention or any intracranial haemorrhage
- Grade 3 or greater non-haematological toxicity at least possibly related to acalabrutinib (including grade 3 or 4 biochemical AEs). The following will be excluded; Grade 3 or 4 nausea in patients who have not received optimal treatment with anti-emetics, Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeal therapy, alopecia and those patients experiencing grade 3 or 4 administration reactions from rituximab.

- Grade 4 thrombocytopenia or neutropenia for more than 7 days despite GCSF use.
- Any complete, continuous dose interruption more than 7 days for acalabrutinib related toxicities of grade 2 or greater within cycle 2.

If a DLT attributed to acalabrutinib per the investigator's assessment occurred, dosing with acalabrutinib will be withheld. Acalabrutinib treatment will be resumed at a lower dose only after toxicity has resolved to  $\leq$  grade 1. There will be no dose re-escalation for acalabrutinib after recovery from toxicity, and no intra-cohort patient dose escalation will be allowed.

Dose adjustments for R-CHOP components, will follow conventional dose modification schedules.

**Table 1** Cohort size Assessment Actions

Cohort size	Assessment	Actions
6 patients	0 DLTs	If cohort 1: proceed to the next cohort and escalate dose If cohort 2: RP2D is established as this dose
6 patients	1-2 DLTs	If cohort 1 or 2: Expand cohort to include up to 12 evaluable patients and re-evaluate
6 patients	$\geq 3$ DLTs	If cohort 1: Dose will be considered non-tolerated dose (NTD) No further recruitment to this cohort and dose escalation will cease If cohort 2: The RP2D will be defined as the dose in the previous cohort or further assessment may be required of an intermediate dose
12 patients	1-2 DLTs	If cohort 1: dose escalation may occur by proceeding to the next cohort, at the safety committee's discretion If cohort 2: RP2D may be established at this dose, at the safety committee's discretion
12 patients	$\geq 3$ DLTs	If cohort 1: Dose will be considered non-tolerated dose (NTD) No further recruitment to this cohort and dose escalation will cease If cohort 2: The RP2D will be defined as the dose in the previous cohort or further assessment may be required of an intermediate dose

#### Phase II: Dose Expansion Population (acalabrutinib RP2D)

Fifteen patients will be recruited for stage 2 of the study. Following informed consent, they will receive 6 cycles of conventionally dosed R-CHOP with the addition of acalabrutinib at the RP2D on cycle 2 onwards.

Patients will not be selected according to predetermination of molecular classification (ABC or GCB) although this will be examined as an exploratory endpoint in the study. Although, based on biology it is anticipated that the ABC DLBCL patients may potentially benefit most from the addition of a Btk inhibitor, the study will not have enough power to determine if there is an interaction with molecular phenotype and this will be addressed in a follow-up phase III study if this study is successful. As a result, all patients with DLBCL, regardless of molecular phenotype will be recruited.

### 3.1 STUDY ENDPOINTS

#### 3.1.1 Primary endpoint

##### Phase I

- Dose limiting toxicity of acalabrutinib combined to R-CHOP

##### Phase II

- ORR of the combination acalabrutinib and R-CHOP
- Safety of the combination acalabrutinib and R-CHOP

#### 3.1.2 Secondary endpoint

- Pharmacokinetic of acalabrutinib, AUC, C<sub>max</sub>, T<sub>max</sub>, half-life T<sub>1/2</sub> and other PK parameter
- ORR of the combination acalabrutinib and R-CHOP according to COO
- 2-yearsPFS; 2-years overall survival.

#### 3.1.3 Tertiary endpoint

- Btk occupancy by acalabrutinib on peripheral blood using fluorescent affinity probe assay.
- Antibody-dependent cell-mediated cytotoxicity of R-CHOP when combined to acalabrutinib, post 1<sup>st</sup> R-CHOP and at day 8, 2<sup>nd</sup> cycle acalabrutinib + R-CHOP.
- CD86 and CD69 expression as a function of BCR activation by flow cytometry.
- Tumour-specific DNA in plasma will be sequenced throughout treatment and compared with lymphoma tissue and clinical course.
- Apply the following techniques to FFPE tumour material: mutational panel, FISH analysis, immunohistochemical analysis for dual protein expression of Myc and Bcl2 and gene expression profiling using whole transcriptome profiling.

### 3.2 DEFINITION OF END OF TRIAL

The end of the study is defined as the date of the last follow-up visit of the last patient (to occur 24 months after receiving the last study treatment) or sooner, if all patients have progressed, died or withdrawn from the study. The study will also terminate early if 3 DLT occur for the first 6 patients in stage 1.

Investigators will be informed when patient recruitment ceases.

The Trial Steering Committee, SRC or DMEC may prematurely discontinue the trial. Any such decision will be notified to the MHRA and REC.

## 4 SELECTION AND ENROLMENT OF PARTICIPANTS

### 4.1 CONSENT

Consent to enter the trial must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

A copy of the signed trial consent form and if used, Tissue Block screening consent form will be sent to SCTU immediately following consent. The consent form will be scanned and sent **from an nhs.net email**

address to uhs.sctu@nhs.net marked FAO ACCEPT trial team. The original signed consent form will be filed in the Investigator Site File.

## 4.2 INCLUSION CRITERIA

- Histologically confirmed DLBCL, expressing CD20. Sufficient tumour block should be available to forward to a central laboratory for gene expression profiling and pathology review. At a minimum, patients should have sufficient tumour material to test for: H/E morphological check of compatibility of DLBCL diagnosis, immunophenotyping & RNA for gene expression profiling.
- Measurable disease of at least 15mm.
- Not previously treated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent
- Stage IAX (bulk defined as lymph node diameter >10cm) to stage IV disease and deemed to require a full course of chemotherapy. Patients with non-bulky IE disease will not be eligible.
- ECOG performance status 0-2 or 3 if this is directly attributable to lymphoma.
- Adequate bone marrow function with platelets  $> 100 \times 10^9/L$ ; neutrophils  $> 1.0 \times 10^9/L$  at study entry, unless lower figures are attributable to lymphoma.
- Measured or calculated creatinine clearance  $> 30 \text{mls/min}$ , (calculated using the formula of Cockcroft and Gault  $[(140 - \text{Age}) \times \text{Mass (kg)} \times (1.04 \text{ (for women) or } 1.23 \text{ (for men)})] / \text{Serum Creatinine } (\mu\text{mol/L})$ ).
- Serum bilirubin  $< 35 \mu\text{mol/L}$  and transaminases  $< 2.5 \times$  upper limit of normal at time of study entry
- Cardiac function sufficient to tolerate  $300 \text{mg/m}^2$  of doxorubicin. A pre-treatment echocardiogram or MUGA is required to establish baseline LVEF equal to or greater than institutional normal range.
- No concurrent uncontrolled medical condition.
- Life expectancy  $> 3$  months.
- Aged 16 years and above.
- Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
- Ability to understand the purpose and risks of the study and provide signed and dated informed consent.

## 4.3 EXCLUSION CRITERIA

Patients will be excluded from the study entry if any of the following criteria are met:

- Previous history of treated or untreated indolent lymphoma. However newly diagnosed patients with DLBCL who are found to also have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.
- Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.
- Diagnosis of primary mediastinal lymphoma.
- Diagnosis of primary Central Nervous System lymphoma.
- History of stroke or intracranial haemorrhage in preceding 6 months.
- History of bleeding diathesis (e.g., haemophilia, von Willebrand disease).
- Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. However, patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible.
- Prior exposure to a BCR inhibitor (e.g. Btk inhibitors, phosphoinositide-3 kinase (PI3K), or Syk inhibitors) or BCL-2 inhibitor (e.g. ABT-199)
- Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
- Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).

- **Patients receiving proton pump inhibitors should switch to short-acting H2-receptor antagonists or antacids prior to study entry to be eligible for enrolment into this study.**
- Uncontrolled systemic infection.
- Major surgery in the preceding 4 weeks of first dose of study drug. If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
- Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec at screening. QTc interval should be calculated using Fridericia's formula.
- Serological positivity for Hepatitis B, C, or known HIV infection. As per standard of care, prior to initiation of immunochemotherapy, the results of hepatitis serology should be known prior to commencement of therapy.
  - Positive test results for chronic HBV infection (defined as positive HBsAg serology) will not be eligible. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) will not be eligible. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible.
  - Positive test results for hepatitis C (HCV antibody serology testing) will not be eligible.
- Women who can bear children must agree to use two highly effective forms of contraception or abstinence during the study and for 12 months after the last treatment dose. Highly effective forms of contraception are defined in Section 4.7.
- Breastfeeding or pregnant women.
- Men who can father children must agree to use two highly effective forms of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose. Highly effective forms of contraception are defined in Section 4.7.
- Men must agree to refrain from sperm donation during the study and for 12 months after the last treatment dose.
- Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.
- Prior malignancy (other than DLBCL), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for  $\geq 2$  years or which will not limit survival to  $< 2$  years. Note: these cases must be discussed with SCTU.
- Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass.
- Any immunotherapy within 4 weeks of 1<sup>st</sup> dose of the study.
- Concurrent participation in another therapeutic clinical trial.

#### **4.4 SCREEN FAILURES**

Patients who are screen failures will have their initials, year of birth and reasons for failure recorded on a screening form.

#### **4.5 REGISTRATION / RANDOMISATION PROCEDURES**

During the initial clinic visit where the main trial information sheet is offered and explained, patients can be given the option to either:

Sign a consent form to allow a historical tissue sample to be sent to HMDS to confirm if enough diagnostic material is available to meet inclusion criteria 1. This consent form must be signed by

an Investigator and the patient. These patients will be required to return later to sign consent for the main trial if it is confirmed there is sufficient tissue and the patient wishes to participate in the ACCEPT trial. The main study consent form must be signed by an Investigator and the patient.

Or

- For those patients whose tissue samples are stored on site and are easily accessible for shipment to HMDS, pre-consent to Tissue Block Screening and storage may not be required, unless local policy dictates that this consent is also required. In these instances patients should be offered the main trial information sheet during their initial clinic visit.

Please send the patients' tumour block (unless already sent after Tissue Block Screening consent was obtained), 2x10ml blood samples, in the Streck tubes and EDTA, immediately to HMDS for analysis on completion of the Informed Consent process. These blood samples need to arrive at HMDS by the next day. Tumour samples must be received prior to Cycle 2 as patient will be considered ineligible if it is not received within this timeframe.

Only patients fulfilling all eligibility criteria should be registered and patients must be registered before cycle 1 of treatment commences. Any queries should be discussed with the SCTU before registration.

To register a patient, you will need to:

1. Complete Cohort Assignment Form
2. Send in the Cohort Assignment Form to SCTU
3. Use the iMedidata Rave database, by completing the eligibility checks and the enrolment stage.
4. Once this is complete the database shall provide you with a unique patient trial ID number.

#### **4.6 CO-ENROLLMENT GUIDELINES**

Patients in the ACCEPT study should not be recruited into other studies of anti-lymphoma treatments prior to disease progression, nor should they be already participating in other trials of anti-lymphoma therapy prior to study entry.

Any queries should be addressed to the ACCEPT Trial Manager.

#### **4.7 CONTRACEPTION**

Contraception is mandated from trial entry until 12 months after the last treatment dose for patients of reproductive potential.

Definitions for women of child bearing potential (WOCBP) and for subjects of non-reproductive potential. WOCBP are women who are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Women are considered to be of non-reproductive potential if they meet any of the following criteria:

- Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormone contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Have had a hysterectomy and/or bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks before screening.
- Have a congenital or acquired condition that prevents childbearing.

Men are considered to be of non-reproductive potential if they are permanently sterile due to bilateral orchidectomy.

Patients with reproductive potential must use two highly effective methods of contraception during the study, with male patients also agreeing to use additional barrier or abstinence due to the risk of exposure to a developing foetus if the female partner is already pregnant. Examples of highly effective methods of contraception include combined or progesterone-only hormonal contraceptives associated with inhibition of ovulation (implants, injectable or oral), intrauterine devices, and intrauterine hormone releasing system, true sexual abstinence, bilateral tubal occlusion, vasectomized partner. Note that barrier methods with and without spermicide, progesterone-only hormonal contraceptives where inhibition of ovulation is not the primary mode of action, periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence for the duration of exposure to IMP or withdrawal are not acceptable methods of contraception.

Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method.

Both male and female patients must be counselled about future fertility prospects and sperm/ovarian preservation prior to study entry. Male patients must refrain from donating sperm once on study and during treatment and the 12 month follow up period. Acalabrutinib is not known to confer long term reduction in fertility, however the cytotoxic drugs used in this protocol, i.e. doxorubicin and cyclophosphamide, may do.

## **5 TRIAL OBSERVATIONS AND PROCEDURES**

### **5.1 SCREENING PROCEDURES**

Patients who have signed the main informed consent form will be evaluated for inclusion and exclusion criteria at the screening visit, which should take place within 14 days before the start of treatment.

The following assessments will take place within 14 days before the first dose of study medication except for a pregnancy test which should be done on day 1 before treatment commences. Investigations performed for the purposes of diagnosis and staging may be used as screening assessments if they have been performed within the appropriate trial window. The PET-CT scan must be within 35 days, serology for Hepatitis B and C and Echocardiogram/MUGA (depending on local policy) may be performed up to 28 days prior to planned therapy, and bone marrow up to 90 days prior to planned therapy.

- Medical history including demographics, previous and concurrent relevant diseases and medications.
- Physical examination.
- Vital signs, including weight, height, blood pressure, pulse and temperature.
- Recording of ECOG performance status.
- 12 lead Electrocardiogram is mandatory for all patients. In addition, an Echocardiogram or MUGA (as per local practice) will be performed for all patients at baseline to establish a left ventricular ejection fraction of >55% and patients should be considered fit enough to receive 300mg/m<sup>2</sup> doxorubicin.
- PET and Contrast Enhanced CT of chest, abdomen and pelvis (neck if indicated) should be carried out within 35 days of planned treatment. The PET-CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality and includes the use of intravenous (IV) contrast. If this cannot be achieved, a PET and separate Contrast Enhanced CT scan should be performed. Bi-dimensional measurements are expected. Bone marrow aspirates and trephine biopsy (single site with adequate trephine) within 90 days of first study treatment.

- Serum chemistry to include sodium, potassium, urea, creatinine, bilirubin, alanine or aspartate transaminase (ALT or AST), alkaline phosphatase, albumin,  $\beta$ 2 microglobulin, LDH, calcium, phosphate, uric acid and immunoglobulins.
- Full blood count with differential including, but not limited to white blood cell count, haemoglobin, haematocrit, platelet count, ANC, and absolute lymphocyte count (ALC)
- Serology for Hepatitis B and C. As per standard of care, prior to initiation of immunochemotherapy, the results of hepatitis serology should be known. In the acute situation, registration may occur without the results of the hepatitis serology but must be available to the SCTU prior to first study treatment.
- Cerebrospinal fluid examination should be performed if clinically indicated or lymphomatous involvement of bone marrow, peripheral blood, nasal/paranasal sinuses or testis. CNS prophylaxis may be given according to local policy.
- Diagnostic tumour block to be forwarded immediately upon obtaining informed consent to HMDS, Leeds, according to study procedure. If tumour block is not received prior to Cycle 2 the participant will not be eligible to continue the study. Unless the tissue block consent form was signed, and tissue sample sent prior to main study screening. A 1x7.5ml EDTA blood sample to be taken and forwarded immediately to HMDS, Leeds.
- A 20ml blood sample to be taken using 2x10ml Streck tube and immediately sent to HMDS, Leeds.

## 5.2 TRIAL PROCEDURES

The following procedures will occur at the time points listed below during Stage 1 and Stage 2 of the ACCEPT study.

### Baseline

- Informed Consent
- Inclusion/Exclusion Check
- Medical History
- Physical Exam
- IPI and NCCN-IPI
- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- PET-CT or contrast enhanced CT with separate PET. Bi-dimensional measurements are expected.
- Bone Marrow Biopsy
- Biochemistry (renal, liver function and additional baseline panel)
- Haematology
- Serology (Hep B and C, HIV)
- Pregnancy Test
- ECG and ECHO/MUGA (depending on local practice)
- Cerebrospinal fluid examination
- Tumour Material, EDTA Sample and Streck Plasma DNA Sample (to be sent to HMDS)
- Concomitant Medications
- Adverse events from consent. Only Adverse events related to the screening procedures should be reported prior to first study treatment.

### Cycle 1

#### Day 1:

- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Concomitant Medications



- Adverse Events

## Cycle 2

### Day 1:

- Physical Exam
- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Pregnancy Test
- Routine laboratory screen – Full blood count, renal and liver function
- PK/PD Samples
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events
- Streck Plasma DNA Sample (to be sent to HMDS)

### Day 8:

- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Routine laboratory screen – Full blood count, renal and liver function
- PK/PD Samples
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

### Day 15:

- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Routine laboratory screen – Full blood count, renal and liver function
- PK Samples
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

## Cycle 3

### Day 1:

- Physical Exam
- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Pregnancy Test
- ECG
- Routine laboratory screen – Full blood count, renal and liver function
- PK Samples
- Immunoglobulins
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events
- Streck Plasma DNA Sample (to be sent to HMDS)

#### Cycle 4

##### Day 1:

- Physical Exam
- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- ECHO
- Pregnancy Test
- Routine laboratory screen – Full blood count, renal and liver function
- PD Samples
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

##### Day 8:

- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Routine laboratory screen – Full blood count, renal and liver function
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

#### Cycle 5

##### Day 1:

- Physical Exam
- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- ECG
- Pregnancy Test
- Routine laboratory screen – Full blood count, renal and liver function
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

#### Cycle 6

##### Day 1:

- Physical Exam
- Vital Signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Pregnancy Test
- Routine laboratory screen – Full blood count, renal and liver function
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

#### Cycle 7

##### Day 1:

- Physical Exam
- Vital signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status

- ECG
- Pregnancy Test
- Routine laboratory screen- Full blood count, renal and liver function
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events
- Contrast-enhanced CT scan to be completed during Week 19 (+/- 1 week). Bi-dimensional measurements are expected.

### Cycle 8

#### Day 1:

- Physical Exam
- Vital signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- Pregnancy Test
- Routine laboratory screen- Full blood count, renal and liver function
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events

### End of Treatment

Response to therapy will be made within 3 weeks from the last dose of study drug.. If patients receive radiotherapy, response assessment should be prior to initiation of radiotherapy.

The following will be performed:

- Physical Exam
- Vital signs (respiration, pulse, blood pressure and temperature)
- ECOG Performance Status
- ECG and ECHO
- Pregnancy Test
- Routine laboratory screen- Full blood count, renal and liver function
- Bone Marrow Biopsy – if initially performed and marrow involved with lymphoma
- Compliance
- Concomitant Medications
- Assessment of toxicity and adverse events
- Streck Plasma DNA Sample (to be sent to HMDS)
- Immunoglobulins
- PET-CT or contrast-enhanced CT and separate PET to be completed within 3 weeks of the patient completing cycle 8.

## **5.3 FOLLOW UP**

Subsequent study visits will be performed at months 3, 6, 9, 12, 16, 20 and 24 following completion of all therapy for patient who does not have confirmed disease progression. A visit window of +/- 2 weeks is permitted.

At each follow-up visit, the following will be performed:

- Physical exam
- ECOG performance status

- Pregnancy Test (at 3,6, 9 and 12 months only)
- Assessment of toxicity and adverse events
- Routine laboratory screen: Full blood count, LDH.
- Adverse Events
- Streck Plasma DNA Sample (to be sent to HMDS)
- Immunoglobulins (at 6, 12 and 24 months only)

Contrast enhanced CT scan of the chest, abdomen and pelvis (and neck if indicated) will be performed at 12 months and 24 months following completion of all therapies, or if clinical suspicion of lymphoma progression. Bi-dimensional measurements are expected.

Patients who have been withdrawn from the study therapy will be followed up from last day of treatment, according to the above schedule, until disease progression is documented, or second-line induction therapy is commenced. In these instances, patients will be followed up for collection of survival data at 12 and 24 months.

#### 5.4 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and /or the study protocol will immediately be reported to the regulatory authorities and other organizations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

#### 5.5 DISCONTINUATION OF TRIAL TREATMENT

In consenting to the study, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the study procedures at any time. The investigator, in consultation with the SCTU, may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Any subject has the right to withdraw from treatment at any time. In addition, patients may withdraw from the treatment for the following reasons:

- Any subject who has **confirmed** objective evidence of cancer progression while receiving R-CHOP + acalabrutinib should be withdrawn from the study treatment. If there is uncertainty regarding whether there is true cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4-week intervals) pending confirmation of progression. Transient worsening of disease early in therapy or during temporary interruption of study therapy (e.g., for drug-related toxicity, surgery, or intercurrent illness) may not indicate cancer progression. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiographic assessment can be attempted to document whether tumour control can be maintained or whether cancer progression has occurred.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the CI. Such patients should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should immediately stop the study treatment.
- Any subject who becomes significantly non-compliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.

Patients withdrawn from trial treatment for reasons other than progression will continue to be followed on the full pathway, according to the protocol, for months 3, 6, 9, 12, 16, 20 and 24. Those that progress will be followed up for survival only. Patient may decline to consent to further follow-up and this must be clearly documented.

Patients who do not complete six cycles of treatment for reasons other than toxicity will be replaced.

### **5.5.1 Reasons for discontinuation of trial treatment**

Participants may be discontinued from the study in the event of:

- Clinical decision, as judged by the Principal Investigator
- Protocol violation
- Toxicity from study therapy
- Patient decision to withdraw from treatment

Full details of the reason for trial discontinuation should be recorded in the eCRF and medical record.

## **5.6 END OF STUDY AND WITHDRAWAL**

The end of study for individual patients will occur when one of the following events take place:

1. The patient reaches the final follow up visit, which will be 2 years after receiving the last study treatment.
2. If the patient is discovered to be ineligible over the course of the study.
3. Patient is lost to follow up.
4. Patient withdrew consent from follow up.
5. Death occurred.

If a patient is lost to follow-up the local Principal Investigator along with the patient's usual clinician should attempt contact. Failing this, the patient's GP will be contacted and requested to provide follow-up information where possible.

Recruitment is expected over a 12 months period, with a follow-up duration of 2 years.

### **Withdrawal**

The participant/legal representative is free to withdraw consent from the study at any time without providing a reason.

Investigators should explain to patients the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, patients who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If patients additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect survival follow-up data and unless the patient explicitly states otherwise, survival follow-up data will continue to be collected.

Details of trial discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

## **6 TREATMENTS**

### **6.1 TREATMENT SCHEDULE**

Treatment will involve 1 cycle of R-CHOP followed by 5 cycles of R-CHOP plus acalabrutinib (as per cohort dose). Cycle 1-6 will be 21 day cycles. Acalabrutinib will commence for cycles 7 and 8 for 56 consecutive

days following day 21 of cycle 6. Sites may administer acalabrutinib prior to R-CHOP on day 1 of each cycle. There is no cessation of treatment between cycle 6 and cycle 7. Dosing for the participant will be the same as they were receiving concomitantly with R-CHOP (determined by the stage of the trial that and cohort assigned to). A contrast enhanced CT scan shall be conducted prior to or at the start of cycle 7.

A pre-phase will be permissible according to individual patient need and local policy. This should not exceed 10 days of Prednisolone 100mg od (or equivalent).

For elderly or poor performance status patients a dose reduction of cyclophosphamide and doxorubicin by 25% will be permissible for cycle 1, at the investigator's discretion. No other cycle 1 dose reductions will be allowed.

### 6.1.1 Stage 1

#### Cycle 1 (R-CHOP)

Drug	Dose	admin	Day				
			1	2	3	4	5
Rituximab	375 mg/m <sup>2</sup>	IV infusion	√				
Cyclophosphamide	750 mg/m <sup>2</sup>	IV bolus	√				
Vincristine	1.4 mg/m <sup>2</sup> (max 2mg)	IV infusion	√				
Doxorubicin	50mg/m <sup>2</sup>	IV bolus	√				
Prednisolone	100mg	oral	√	√	√	√	√

#### Cycle 2-6 (R-CHOP + acalabrutinib)

Drug	Dose	admin	Day				
			1	2	3	4	5
Rituximab	375 mg/m <sup>2</sup>	IV infusion	√				
Cyclophosphamide	750 mg/m <sup>2</sup>	IV bolus	√				
Vincristine	1.4 mg/m <sup>2</sup> (max 2mg)	IV infusion	√				
Doxorubicin	50mg/m <sup>2</sup>	IV bolus	√				
Prednisolone	100mg	oral	√	√	√	√	√
Acalabrutinib	According to cohort	oral	Day 1-21				

To ensure subject compliance, on the days the patients attend clinic for their pre-dose PK/PD measurements will receive their morning acalabrutinib dose in the clinic.

Proposed acalabrutinib dosing cohorts:

Cohort number	Acalabrutinib dose
1	100 mg od
2	200 mg (100 mg bd)

**Cycle 7-8 (acalabrutinib only)**

Drug	Dose	admin	Cycle 7	Cycle 8
			(28 days)	(28 days)
Acalabrutinib	100mg od for cohort 1	oral	Day 1-28	Day 1-28
Acalabrutinib	100mg bd for cohort 2	oral	Day 1-28	Day 1-28

**6.1.2 Stage 2**

Fifteen patients will be registered for stage 2 of the study and treated to the following regimen. This dose expansion cohort will allow for further safety data to be collected.

**Cycle 1 (R-CHOP only)**

Drug	Dose	admin	Day				
			1	2	3	4	5
Rituximab	375 mg/m <sup>2</sup>	IV infusion	√				
Cyclophosphamide	750 mg/m <sup>2</sup>	IV bolus	√				
Vincristine	1.4 mg/m <sup>2</sup> (max 2mg)	IV infusion	√				
Doxorubicin	50 mg/m <sup>2</sup>	IV bolus	√				
Prednisolone	100 mg	oral	√	√	√	√	√

**Cycle 2-6 (R-CHOP + acalabrutinib)**

Drug	Dose	admin	Day				
			1	2	3	4	5
Rituximab	375 mg/m <sup>2</sup>	IV infusion	√				
Cyclophosphamide	750 mg/m <sup>2</sup>	IV bolus	√				
Vincristine	1.4 mg/m <sup>2</sup> (max 2mg)	IV infusion	√				
Doxorubicin	50mg/m <sup>2</sup>	IV bolus	√				
Prednisolone	100mg	oral	√	√	√	√	√
Acalabrutinib	RP2D	oral	Day 1-21				

### Cycle 7-8 (acalabrutinib only)

Drug	Dose	admin	Cycle 7	Cycle 8
			(28 days)	(28 days)
Acalabrutinib	RP2D	oral	Day 1-28	Day 1-28

#### 6.1.3 Continuation of Study Therapy

Patients will receive R-CHOP only at cycle 1 and of R-CHOP + acalabrutinib from cycle 2-6. This will be followed by two 28 days cycle of acalabrutinib only for a total of 56 days. There will be no provision for treatment beyond 8 cycles.

If the patient is felt to clinically require further therapy upon completion of study treatment, this will be documented under “second line induction therapy”. Those patients will be followed up for survival only at years 1 and 2 post treatment. Any additional therapy will be at the discretion of the local Investigator.

## 6.2 SUPPORTIVE CARE

Live vaccination whilst on rituximab is prohibited and for patients who have peripherally B cell depletion must not have a live vaccination within three months of last rituximab dose.

Patients will receive standard anti-emetic as per local policy.

Allopurinol 300mg orally od should be given as per local practice. Rasburicase may be administered if high risk of tumour lysis syndrome.

Mouth care therapies are given according to local policy.

Antacids and calcium supplements should be avoided for a period of at least 2 hours before and after taking acalabrutinib. Short acting H2 receptor antagonists should only be taken at least 2 hours following acalabrutinib administration.

Diarrhoea and constipation are both recognised side effects of therapy in this protocol, diarrhoea is the most common. Treatment should be given according to local policy, although prophylactic anti-diarrhoeal agents are not recommended.

GCSF is mandated for all patients receiving R-CHOP and acalabrutinib. The formulation and duration will be according to local policy for primary prophylaxis but should be for at least seven days or until neutrophil recovery for those patients receiving the non-pegylated formulation (see table of section 6.9.1.1).

Antimicrobial prophylaxis given against *Pneumocystis jirovecii* pneumonia (PCP) is mandated (see section 6.6.3 for more information).

Suitable infective prophylaxis to be given to patient's aged 65 and over as per local policy. Ciprofloxacin prophylaxis should be avoided due to possible interactions with acalabrutinib.

## 6.3 DIETARY RESTRICTIONS

Acalabrutinib can be taken with or without food. Because acalabrutinib may be metabolized by CYP3A4, patients should be strongly cautioned against consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A4 inhibitors) or using herbal remedies or dietary supplements (in particular, St John's Wort, which is a potent CYP3A4 inducer).



Otherwise patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhoea, nausea or vomiting.

## **6.4 IMP SUPPLY**

Acalabrutinib will be centrally supplied free of charge for this clinical trial by ACERTA Pharma. Sites will order acalabrutinib via the Southampton Clinical Trials Unit. ALMAC Clinical Supplies (on behalf of ACERTA Pharma) will pack, label, QP release and distribute the IMP for the study to participating sites.

Only those supplies intended for use in the study should be dispensed to study participants and clinical trial supplies must be dispensed in accordance with the study protocol.

Other study treatments are standard of care and will be from local supplies. Please see Pharmacy Manual for further information on IMP.

## **6.5 ADMINISTRATION**

Investigators are prohibited from supplying acalabrutinib to any patients not properly enrolled in this study or to any physicians or scientists except those designated as sub investigators on Site Delegation Log. The investigator must ensure that patients receive acalabrutinib only from personnel who fully understand the procedures for administering the drug.

For cohort 1 acalabrutinib is intended to be administered orally once daily. Cohort 2 of patients are intended to be administered orally twice daily with the second daily dose 11 to 13 hours after the first dose. Acalabrutinib should be taken with 240 ml of water (avoid grapefruit and Seville orange juices due to CYP3A4 inhibition). The capsule should be swallowed intact and patients should not attempt to open capsules or dissolve them in water.

If a dose is not taken within the allowed window it can be taken up to 3 hours after the scheduled time with a return to the normal schedule for the next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 6.8.

For treatments that are taken in the clinic, patients should take the dose from the drug dispensed for them for that particular time period. To assure subject compliance of 80% or more, patients will receive a diary to record the specific time each dose has been taken and to record reasons for any missed doses. Subject compliance will be assessed at every visit. The patients will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded. Returned capsules must not be re-dispensed to another patient.

### **6.5.1 Overdose Instructions for Acalabrutinib**

For any subject experiencing an acalabrutinib overdose (accidental or intentional use of the drug in an amount higher than the dose being studied), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and haematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

**SCTU must be contacted immediately if a study drug overdose occurs for onward reporting requirements.**

### **6.5.2 Treatment Compliance**

Subject compliance with acalabrutinib will be assessed at each study visit. Compliance will be assessed by the investigator and/or study personnel at each visit using direct questioning, examination of subject drug administration diaries, or pill counts.

### **6.5.3 Warning and Precautions**

#### Haemorrhage

Serious haemorrhagic events, including central nervous system, respiratory and gastrointestinal hemorrhage, have been reported in clinical trials with acalabrutinib; some of these bleeding events resulted in fatal outcomes. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with haematological malignancies. The mechanism for hemorrhage is not well understood. Acalabrutinib may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on the surgery and risk of bleeding.

#### Infections

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, have been reported in clinical studies with acalabrutinib. The most frequently reported Grade 3 or 4 infection was pneumonia. Monitor patients for signs and symptoms of infection and treat as medically appropriate. Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) have occurred in subjects with hematologic malignancies.

- Serious or life-threatening reactivation of viral hepatitis may occur in patients treated with acalabrutinib. Please refer to Section 4.3 for details on viral hepatitis screening for this study.
- Serious or life-threatening occurrence of PML may occur in subjects treated with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioural changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties. If PML is suspected, hold further study treatment (as applicable, based on risks in the Investigator Brochure or local prescribing information) until PML is excluded. A diagnostic evaluation may include (but is not limited to):
  - Neurologic consultation
  - Brain MRI
  - PCR analysis for John Cunningham or JC virus DNA in cerebrospinal fluid.

If PML is confirmed, permanently discontinue study treatment (as applicable, based on risks in the Investigator Brochure of local prescribing information).

#### Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Subjects should be closely monitored as appropriate.

#### Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer. Advise protection from sun exposure.

#### Atrial Fibrillation

Events of atrial fibrillation/flutter have been reported in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation. The mechanism for atrial fibrillation is not well understood.

## **6.6 ADDITIONAL THERAPY FOR DLBCL**

Additional therapy for DLBCL may be given according to local policy in the following manner:

### **6.6.1 Central nervous system prophylaxis**

Patients with lymphomatous involvement in bone marrow, peripheral blood, nasal/paranasal sinuses, orbit, paravertebral disease and testis are considered to have high risk for CNS disease as are those with a high LDH and multiple extra-nodal sites. They should receive prophylactic intrathecal methotrexate at 12.5mg per cycle for between three to six cycles, but this is at the Investigators discretion and according to local policy. The acalabrutinib + R-CHOP protocol is permissive, and CNS intrathecal prophylaxis should be according to their local policy. Intrathecal methotrexate must always be administered after all intravenous drugs are given. This should be administered according to local and national policies.

The use of prophylactic systemic administration of methotrexate is not permissible for patients during acalabrutinib + R-CHOP therapy, however may be considered at the end of therapy following discussion between the PI and SCTU.

### **6.6.2 Radiotherapy**

Following the last cycle of acalabrutinib + R-CHOP, the use of radiotherapy to initial bulk disease, extra-nodal sites or residual disease is left to individual Investigator's discretion.

If patients receive radiotherapy, response assessment should be prior to initiation of radiotherapy.

### **6.6.3 *Pneumocystis jirovecii* pneumonia (PCP) Prophylaxis**

During treatment with acalabrutinib, patients should receive antimicrobial prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP). Local guidelines should be taken into account but co-trimoxazole is recommended. Dapsone, pentamidine nebulisers and atovaquone are suitable alternatives. None of these are contra-indicated with acalabrutinib or R-CHOP.

## **6.7 ACCOUNTABILITY**

The Principal Investigator (PI) is fully responsible for the Investigational Medicinal Products (IMPs) at the site. The IMPs must not be used outside the context of this protocol. Dispensing of medication may be delegated to a hospital pharmacy as locally applicable. The person responsible for dispensing the medication will be responsible for maintaining adequate control of the IMPs and for documenting all transactions relating to them (as a minimum batch number, expiry date and dispense date must be documented on the Drug Accountability Logs). IMPs accountability must be maintained and readily available for inspection by representatives of SCTU, Sponsors, Acerta Pharma or regulatory authorities at any time. IMPs must be stored in a safe and secure place (only accessible to authorized personnel), and proper dispensing arrangements must be made.

An Investigational Medicinal Product Accountability Log must be used. For accurate accountability, the following information must be noted when IMP supplies are used during the study:

- Study identification number
- Subject initials
- Batch number of acalabrutinib dispensed for that subject
- Date and quantity of drug dispensed
- Any unused drug returned by the subject

Please refer to Pharmacy Manual for more detailed instruction on IMP accountability.

## 6.8 PROHIBITED THERAPIES

Acalabrutinib is not a strong direct inhibitor or inducer of CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug interaction at the level of inhibition or induction of CYP isoforms. Acalabrutinib is partially metabolised by CYP3A; its exposure is affected when co-administered with strong CYP3A4 inducers or inhibitors. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 5 and refer to Pharmacy Manual) should be avoided when possible.

Based on these considerations, patients who require therapy with drugs listed in Appendix 5 should not be enrolled into the study. If medically justified, patients may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A4 while on study, monitor the subject closely for potential drug-related toxicities.

The effect of agents that reduce gastric acidity (e.g., proton pump inhibitors, H2 receptor antagonists or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE HV-004). Results from this study indicate that patients should avoid the use of calcium carbonate containing drugs or supplements (e.g., antacids and calcium supplements) for a period of at least 2 hours before and after taking acalabrutinib. **Similarly, patients should avoid the use of H2-receptor antagonists for a period of 2 hours after taking the study drugs.** Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors (see Appendix 8) while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, if a subject requires the use of a proton pump inhibitor while on study (e.g., to treat a gastric ulcer) please discuss treatment options with SCTU.

In circumstances where treatment with ciprofloxacin is needed, the dose of acalabrutinib should be reduced to 100mg od.

Warfarin and equivalent Vitamin K antagonists are prohibited. However patients may use therapeutic low molecule weight heparin or low dose aspirin.

## 6.9 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY

### 6.9.1 Haematological Toxicity

#### 6.9.1.1 Neutropenia

Problem	Action
Neutrophils < 1.0x10 <sup>9</sup> /L on day 1 of cycle	Delay therapy until neutrophil recovery >1.0x10 <sup>9</sup> /L. If not recovered after 14 days, withdraw patients from study. GCSF permissible as secondary prophylaxis according to local policy

Grade 4 neutropenia leading to infection despite GCSF support	Reduce dose of cyclophosphamide and doxorubicin by 75% for all subsequent cycles and hold acalabrutinib until recovery to grade $\leq 1$ or baseline
Grade 4 neutropenia recurs despite 75% dose reduction in cyclophosphamide and doxorubicin	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles and hold acalabrutinib until recovery to grade $\leq 1$ or baseline.
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin.	Withdraw from further study related therapy.

#### 6.9.1.2 Thrombocytopenia

Problem	Action
Platelets $<100 \times 10^9/L$ on proposed day 1 of cycle	Delay therapy until platelets $>100 \times 10^9/L$ . If not recovered after 14 days, withdraw patient from study related therapy.
Grade 4 thrombocytopenia following any cycle of acalabrutinib + R-CHOP with a duration greater than 5 days	Reduce dose of cyclophosphamide and doxorubicin by 75% for all subsequent cycles and hold acalabrutinib until recovery to grade $\leq 1$ or baseline
Grade 4 thrombocytopenia recurs despite 75% dose reduction in cyclophosphamide and doxorubicin with a duration greater than 5 days.	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles and hold acalabrutinib until recovery to grade $\leq 1$ or baseline .
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin with a duration greater than 5 days.	Withdraw from further study related therapy.

#### 6.9.2 Non haematological toxicity

Problem	Action
Grade 3 or 4 nausea, vomiting despite optimal antiemetic therapy	If 1 <sup>st</sup> or 2 <sup>nd</sup> occurrence, hold R-CHOP + acalabrutinib until recovery to grade $\leq 1$ or baseline. May restart at original dose level If 3 <sup>rd</sup> occurrence, hold acalabrutinib until recovery to grade $\leq 1$ or baseline. Restart at a lower dose If 4 <sup>th</sup> occurrence, discontinue acalabrutinib
Grade 3 or 4 diarrhoea despite optimal anti-diarrheal therapy	
Any grade 4 or unmanageable grade 3 toxicity	

#### 6.9.3 Modification for neuropathic pain or peripheral neuropathy

If neurological toxicity due to vincristine appears as grade  $\geq 2$  motor or grade  $\geq 3$  sensory, the dose of vincristine will be reduced to 1mg per cycle. If the neurological toxicity increases despite dose reduction, then vincristine will be stopped.

#### 6.9.4 Cardiac Toxicity

If LVEF has decreased substantially from baseline, as exhibited by repeated ECHO scans, e.g. by  $>20$  points to a final value  $>50\%$  or by  $>10$  points to a final value of  $<50\%$ , the benefit of the continuing the doxorubicin therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

### 6.9.5 Other non-haematological toxicity

Dose reduction of individual medications can be considered if other toxicities such as severe mucositis occur, as per usual local practice. Grading of adverse event precipitating dose reduction should be recorded. Dose reductions for hepatic or renal impairment should be according to local policy.

Special consideration regarding urinary tract toxicity of cyclophosphamide in regards to the following: haemorrhagic cystitis, pyelitis, ureteritis and haematuria must be reported appropriately.

### 6.10 OTHER ACALABRUTINIB TOXICITY

Patients should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a subject experiences acalabrutinib-related DLT or other intolerable AE during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilises to an acceptable degree.

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade  $\leq 1$ . If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for  $\geq 4$  weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. However, the maximum dose of acalabrutinib is 100mg bd for this protocol.

Acalabrutinib has a low risk of phototoxicity therefore the investigator must advise patients to minimise exposure to UV light for the duration of the study treatment and for two weeks after last dose of acalabrutinib.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially acalabrutinib-related toxicity that is Grade  $\geq 3$  in severity. Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with SCTU. Study drug may be withheld for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting  $> 28$  days, unless reviewed and approved by the SCTU.

**Note:** temporary withholding of acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms (refer to Section 5.5 Discontinuation of Trial Treatment for more information on assessing disease progression under these circumstances).

### 6.11 SAFETY ASSESSMENT

Safety will be assessed throughout:

- The reporting of adverse events using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) as described in Appendix 4.
- Regular haematological and biochemistry evaluation
- The dose limiting toxicities (DLT) defined using the NCI CTCAE v4.03.

### 6.12 CONCOMITANT MEDICATIONS

Information on any treatment received by the participant, along with dose, frequency and therapeutic indication, from prior to starting trial treatment up to after the last dose of acalabrutinib will be recorded in the electronic case report form (eCRF).

## 7 STUDY SAMPLING

### 7.1 PHARMACOKINETIC SAMPLING

Acalabrutinib pharmacokinetic will be assessed in all patients by determination of serum concentrations of acalabrutinib by a fully validated assay that has already been used in human studies. The samples will be taken from patient as explained in the following table.

Cycle	Day	Predose	Hours post dose					
			0.5	0.75	1	2	4	6
2	1	X	X	X	X	X	X	X
	8	X	X	X	X	X	X	X
	15	X	X	X	X			
3	1	X						

Post dose samples should be taken at the above specified times  $\pm$  5 minutes after study drug administration.

### 7.2 PHARMOCODYNAMIC SAMPLING

Acalabrutinib PD will be assessed in all patients by measurements of the following:

1. Evaluation of BTK occupancy in peripheral blood mononuclear cells (PBMCs).

PBMC will be incubated with a fluorescently-tagged analogue of acalabrutinib. Acalabrutinib and the probe bind covalently to Btk, with binding of the probe being prevented by acalabrutinib occupancy. Probe-binding will be detected by flow cytometry. PMBCs will be collected by blood sample on day 1 of cycle 2 pre-dose and at 4 hours post-dose and on day 8 of cycle 2 pre-dose, at 2 and 4 hours post dose.

2. Impact of the addition of acalabrutinib on R-CHOP mediated ADCC

Blood samples will be collected on day 1 and day 8 cycle 2 pre- dose and 4 hours post dose. A fluorescent dye release assay measuring target cell lysis, coupled with flow cytometry will be employed to measure ADCC.

3. BCR activation before and after R-CHOP + acalabrutinib

Blood samples for measurement of BCR activation will be collected on day 1 and day 8 cycle 2 pre-dose and on day 1 cycle 4 pre-dose. BCR activation will be determined by measurement of CD86 and CD69 expression on PBMC by flow cytometry.

	Baseline	Cycle			Hours post dose
		Cycle	Day	Predose	4
BTK occupancy PBMCs		2	1	X	X
		2	8	X	
ADCC		2	1	X	X
		2	8	X	X
CD86 and CD69 expression PBMCs		2	1	X	
		2	8	X	
		4	1	X	

The post dose sample should be taken 4 hours  $\pm$  5 minutes after study drug administration.

### 7.3 TRANSLATIONAL RESEARCH

This study will prospectively validate the cell of origin (ABC versus GCB) model of DLBCL and its practicality and utility, as well as assessing the benefit/toxicity of the addition of acalabrutinib to R-CHOP.

- For all patients, sufficient diagnostic material should be available to forward to a central laboratory for pathological review and gene expression profiling. Formalin-fixed paraffin embedded (FFPE) lymph node biopsies should be forwarded to HMDS where molecular phenotyping will be performed by using a reliable array platform requiring the extraction of RNA. Central pathological review will be performed as quality check but not fed back to site unless findings untoward. There must be sufficient tumour block to test for H/E morphological check of compatibility of DLBCL diagnosis, Immunophenotyping, RNA for Gene expression profiling. Additional material will be used for immunohistochemical, cytogenetic and molecular genetic studies FISH, DNA for mutation, TMA. Material will only be retained if the sample size is sufficient for removal of material without compromising its value as archived diagnostic material. This may include the generation of extended full section immunohistochemical studies, tissue microarrays and DNA extraction. The remaining FFPE block will be returned to local pathologist.

DNA extracted from tumour material will be used to perform mutation detection on BCR pathway (e.g. Btk, PI3K, CD79b). Genetic abnormalities of BCR pathway will be correlated with clinical outcomes and the expression of BCR pathway target genes.

## 8 SAFETY

### 8.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

**Adverse Event (AE):** any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

**Adverse Reaction (AR):** all untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product 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.

**Unexpected Adverse Reaction:** an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

*When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*



**Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- **Important medical events\*\*\*.**

\*‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

\*\* Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

\*\*\* Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via the study drug must be reported to the SCTU on the SAE/SUSAR Report Form.

**Note:** *It is the responsibility of the PI or delegate to grade an event as ‘not serious’ (AE) or ‘serious’ (SAE).*

**Suspected Unexpected Serious Adverse Reaction (SUSAR):** any suspected adverse reaction related to an IMP that is both unexpected and serious.

### **Potential Drug Induced Liver Injury (DILI)**

Potential drug induced liver injury is defined as:

- 1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)  
AND
- 2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),  
AND
- 3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

## **8.2 SERIOUSNESS**

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All adverse events that fulfil the criteria definition of ‘serious’ in protocol section 8.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

All SAEs must be reported immediately by the PI at the participating centre to the SCTU.

### 8.2.1 Exceptions:

For the purposes of this trial, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Relapse and death due to Diffuse Large B-Cell Lymphoma
- Hospitalisations for elective treatment of a pre-existing condition that has not worsened.

Patients experiencing grade 4 neutropenia or grade 4 thrombocytopenia without hospitalisation will not need to be reported as an SAE per Chief Investigator decision that neutropenia in this study is not usually life-threatening. If local investigator believes neutropenia is life-threatening for any subject or an important medical event, a SAE should still be submitted.

**All patients hospitalised with grade 4 neutropenia or grade 4 thrombocytopenia should be reported as an SAE.**

## 8.3 CAUSALITY

A complete assessment of the causality must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform Southampton Clinical Trials Unit (SCTU) who will notify the Chief Investigator. Pharmaceutical companies and/or other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the Investigator and others, SCTU will classify the event as per the worst case classification and if onward reporting is required, the MHRA will be informed of both parties' points of view.

Relationship	Description	Denoted
<b>Unrelated</b>	There is no evidence of any causal relationship	SAE
<b>Unlikely</b>	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). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	SAE
<b>Possible</b>	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). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	SAR/ SUSAR
<b>Probable</b>	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR
<b>Definitely</b>	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

## 8.4 EXPECTEDNESS

Expectedness assessments are made against the approved reference safety information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	IB/SmPC	IB/SmPC Section /Table No.	Manufacturer	Date of text revision DD-MMM-YYYY	EMC Last Update
Acalabrutinib	IB Edition 8	Table 36	Acerta Pharma	22-Mar-2019	
Rituximab	SmPC	4.8	Roche Products Limited	11-MAR-2019	18-MAR-2019
Cyclophosphamide	SmPC	4.8	Baxter Healthcare Ltd	07-JUN-2016	29-JUN-2016
Doxorubicin	SmPC	4.8	Medac GmbH	31-OCT-2017	22-AUG-2018
Vincristine	SmPC	4.8	Hospira UK Ltd	OCT-2018	17-OCT-2018
Prednisolone	SmPC	4.8	Accord UK Limited	14-FEB-2018	22-MAR-2018

The nature or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AE should be recorded as 'unexpected'.

## 8.5 REPORTING PROCEDURES

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 SCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

### 8.5.1 Reporting Details

An SAE/SUSAR Report form should be completed for all SAEs, SARs and SUSARS and faxed to SCTU within 24 hours of becoming aware of the event.

Complete the SAE/SUSAR form and fax or email a scanned copy of the form with as many details as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

**Or**

Contact SCTU by phone for advice and then fax or email a scanned copy of the completed SAE/SUSAR form.

### SAE REPORTING CONTACT DETAILS

*Please email or fax a copy of the SAE form to  
SCTU within 24 hours of becoming aware of the event*

**Fax: 0844 774 0621 or Email: [ctu@soton.ac.uk](mailto:ctu@soton.ac.uk)**

FAO: Quality and Regulatory Team

***For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)***

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

### **8.5.2 Follow Up and Post-trial SAEs**

The reporting requirement for SAEs affecting participants applies for all events occurring up to 30 days after the last administration of trial drugs.

All unresolved adverse events should be followed by the investigator until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

### **8.5.3 Non-serious AEs**

All adverse events should be recorded in the relevant eCRF and submitted to SCTU.

### **8.5.4 Pre-existing Conditions**

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the condition worsens during the trial. The condition, however, must be reported on the Medical History eCRF. Any adverse events which occur after informed consent taken should be recorded on the AE eCRF as per safety reporting section.

### **8.5.5 Serious Adverse Events and Reactions**

All SAEs, SARs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE/SUSAR form asks for nature of event, date of onset, severity, corrective therapies given, outcome, causality (i.e. unrelated, unlikely, possible, probably, definitely) and expectedness. The responsible investigator should assign the causality and expectedness of the event with reference to the approved IMP IB/SmPC. The event term should be in accordance with the latest version of MedDRA and grades given in accordance with the NCI CTCAE v4.03. Additional information should be provided as soon as possible if the event/reaction has not resolved at the time of reporting.

### **8.5.6 Pregnancy**

If a participant or their partner becomes pregnant whilst taking part in the trial or in the 12 months following the last dose of treatment the investigator must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible side effects on the foetus. Consent must be sought for the follow-up of the pregnancy using Pregnancy Consent Form.

The investigators must notify the SCTU of this event via the Pregnancy Report Form in iMedidata Rave within 24 hours of site becoming aware. A call should also be made to the Trial Manager to notify SCTU of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be completed.

Follow-up is, of course, dependent on obtaining informed consent for this from the participant (or their partner in the case of male trial participants). Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Report Form. In order for the sponsor or designee to collect any pregnancy information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

If the participant leaves the area, their new healthcare professional should also be informed.

Should the outcome of the pregnancy result in still birth, neonatal death, spontaneous abortion, or birth defects, an SAE/SUSAR Report Form will need to be completed and submitted to the SCTU within 24 hours of site becoming aware.

#### **8.5.7 Overdose**

Study drug overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied.

Any study drug overdose or incorrect administration should be noted and reported to the SCTU via iMedidata RAVE on the AE Form. Should the event meet the serious criteria, this must be reported on the SAE/SUSAR Report Form within 24 hours of becoming aware.

In the event of subject ingestion of more than the recommended acalabrutinib dose, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

### **8.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC**

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit all safety information to the REC in annual progress report.

### **8.7 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA**

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit the Developmental Safety Update Reports to MHRA annually.

## **9 STATISTICS AND DATA ANALYSES**

### **9.1 SAMPLE SIZE**

There is no formal sample size calculation given the modified 6+6 classical design. Sample size for stage 1 is based upon anticipated numbers to complete schedule of dose escalation to DLT or MAD (n=6 - 24 patients). For stage 2, the sample size (n=15) permits sufficient numbers of patients to gain additional safety information and to look for exploratory signal of efficacy in biological subgroups in a pooled analysis of both stages.

### **9.2 INTERIM ANALYSIS**

In stage 1 the SRC will review safety data and advise on dose escalation as per section 3.

In stage 2 an independent DMEC will review outcome and safety data regularly during the trial advising the independent trial steering committee on continuation of the trial.

### **9.3 STATISTICAL ANALYSIS PLAN (SAP)**

The trial will be analysed using the principles of ICH GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations. A full and detailed statistical analysis plan will be developed prior to the final analysis of the trial. The main features of the statistical analysis plan are included below.

All patients who receive any component of therapy will be included in the analysis.

Data will be presented in a descriptive fashion with summary statistics. Means and standard deviations will be reported for continuous outcomes (if data is skewed medians and ranges will be presented) and frequencies and percentages for binary outcomes. Kaplan-Meier survival curves will be produced for the time to event outcomes of PFS and overall survival.

All adverse events (AEs) and serious adverse events (SAEs) by relatedness will be listed and summarised by the CTCAE System Organ Class and term.

### **9.4 FINAL ANALYSIS**

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have had the opportunity to complete protocol defined therapy and have completed the final follow-up visit or sooner, if all patients have progressed, died or withdrawn from the study.

## **10 REGULATORY**

### **10.1 CLINICAL TRIAL AUTHORISATION**

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

## **11 ETHICAL CONSIDERATIONS**

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the study without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

### **11.1 SPECIFIC ETHICAL CONSIDERATIONS**

The SCTU uses the electronic data capture tool called RAVE, which will be used in the ACCEPT trial for sites to input anonymised trial data. The servers that this database will be held on are based in the USA and therefore being stored outside of the UK and EEA. The Patient Information Sheet and Informed Consent Form shall highlight to patients where the data shall be held.

The trial shall also be collecting tumour and blood samples that shall be exported out of the UK. The tumour sample and a number of blood samples shall be sent to the Netherlands to be analysed by the funder's lab. All PK samples collected within this trial are going to be shipped and stored at a third-party lab in the USA. All data that is shipped to the USA and Netherlands will hold no personal data and will remain anonymous. All appropriate contracts and shipping requirements shall be met, and patients shall be informed through the use of the Patient Information Sheet and Informed Consent Form.

## **11.2 ETHICAL APPROVAL**

The study protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

## **11.3 INFORMED CONSENT PROCESS**

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

## **11.4 CONFIDENTIALITY**

SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs participants will not be identified by their names, but by an identification code.

# **12 SPONSOR**

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

## **12.1 INDEMNITY**

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

## **12.2 FUNDING**

The ACCEPT trial is funded through an unrestricted grant from Acerta Pharma (the manufacturer and supplier of acalabrutinib) and endorsed by Cancer Research UK New Agents Committee.

### **12.2.1 Site payments**

The payments assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

The study is adopted onto the NIHR portfolio.

### **12.2.2 Participant payments**

Participants will not be paid for participation in this study.

## **12.3 AUDITS AND INSPECTIONS**

The study may be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

## **13 TRIAL OVERSIGHT GROUPS**

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

### **13.1 TRIAL MANAGEMENT GROUP (TMG)**

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The ACCEPT TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

### **13.2 TRIAL STEERING COMMITTEE (TSC)**

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The ACCEPT TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

### **13.3 SAFETY REVIEW COMMITTEE (SRC)**

The Safety Review Committee will include the CI, sponsor representative, members of the Trial Management Group and a non-voting member of ACERTA Pharma

In phase I the SRC will meet when there are at least 6 evaluable patients at a dose level. All 6 patients must have completed treatment up to the end of cycle 2. The SRC will assess the safety, tolerability and PK results (if available) of acalabrutinib from this cohort to make a decision as detailed below:

- Proceed with dose escalation
- Expand the cohort to a maximum of 6 evaluable patients
- Define the RP2D



- Stop the dose escalation part of the study

#### **13.4 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)/DATA MONITORING AND ETHICS COMMITTEE (DMEC)**

*(NB for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the IDMC/DMEC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The ACCEPT IDMC/DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC/DMEC, including the timing of meetings, methods of providing information to and from the IDMC/DMEC, frequency and format of meetings, statistical issues and relationships with other trial committees.

### **14 DATA MANAGEMENT**

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Informed Consent Form will specify the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to current data protection regulations.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the study team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

## **14.1 DATA SHARING**

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. At a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, [www.southampton.ac.uk/ctu](http://www.southampton.ac.uk/ctu)] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

## **15 MONITORING**

### **15.1 CENTRAL MONITORING**

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Discrepancies found in the data, will be returned to the site for resolution in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

### **15.2 CLINICAL SITE MONITORING**

Before the study can be initiated, the prerequisites for conducting the study must be confirmed and the organisational preparations made with the trial centre. The suitability of the Investigator's research team, technical facilities and availability of eligible patients at the trial centre must be ensured. The Investigator must ensure that all study information is disseminated continuously to all those who are involved. The sponsor, via the Southampton Clinical Trials Unit (SCTU), must be informed immediately of any change in the persons involved in the conduct of the study at site.

The study will be monitored and audited in accordance with the Sponsor and SCTU procedures. All trial-related documents will be made available on request for monitoring and audit by the Sponsor, SCTU, and the relevant ethics committee and for inspection by the MHRA or other relevant bodies. During the trial the Sponsor is responsible for monitoring data quality. Prior to the study start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification prior to each monitoring visit as per monitoring plan.

It is the duty of the Sponsor and SCTU to review study records and compare them with source documents; discuss the conduct of the study and any emerging problems with the Investigator; check that the drug storage and dispensing are reliable and appropriate and verify that the available facilities remain acceptable.

At the final close-down visit, SCTU will clarify any open questions, verify that all data requested, and corrections have been entered correctly on the CRFs and collect the study material that is no longer

required. All unused drug supplied will be destroyed as instructed by the SCTU and destruction certificates retained in the Investigator Site File and a copy sent to SCTU.

#### **15.2.1 Source Data Verification**

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account current data protection regulations). Access should also be given to study staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

### **15.3 SOURCE DATA**

Source documents are where data is first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

## **16 RECORD RETENTION AND ARCHIVING**

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 25 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

## **17 PUBLICATION POLICY**

Data from all centres will be analysed together and published as soon as possible.

Individual Investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of Investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors, then a 'writing committee' will be identified.

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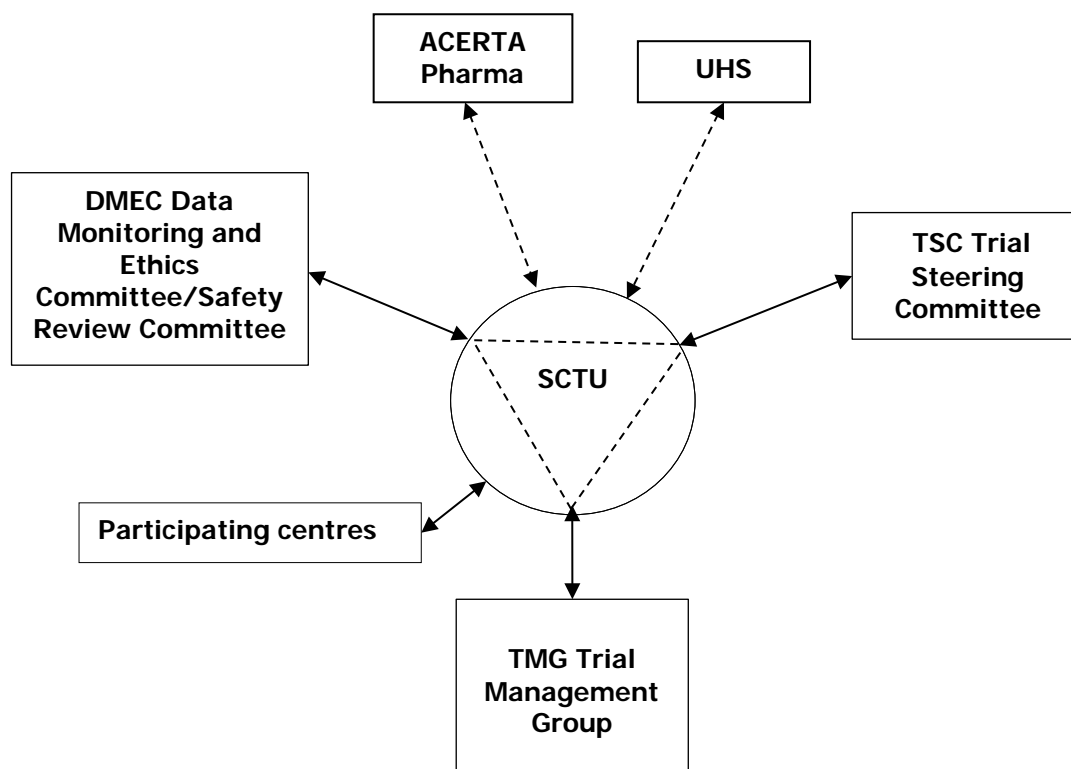
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## 19 APPENDICES

### APPENDIX 1 – COMMUNICATION AND RELATIONSHIP BETWEEN PARTIES



## APPENDIX 2 – ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.:

*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

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Revised: July 27, 2006



### APPENDIX 3 – INTERNATIONAL PROGNOSTIC INDEX AND NCCN-IPI

#### IPI

The adverse factors used to calculate the International Prognostic Index (IPI) are listed below. Score one point for each criterion met.

#### Adverse factors

Parameter	Adverse Factor
Age	>60 years
Ann Arbor stage	III- IV
ECOG performance status	>1
Serum LDH level	>ULN
Number of extra-nodal sites	>1

Patients are assigned to one of four risk group based upon the number of presenting risk factors:

Risk group	Score
Low	0 or 1
Low Intermediate	2
High Intermediate	3
High	4 or 5

## NCCN IPI

NCCN-IPI	Score
<b>Age, years</b>	
>40 to ≤60	1
>60 to ≤75	2
>75	3
<b>LDH, normalised</b>	
>1 to ≤3	1
>3	2
<b>Ann Arbor stage III-IV</b>	1
<b>Extranodal disease<sup>*</sup></b>	1
<b>Performance status ≥2</b>	1

Risk group	Score
Low	0 or 1
Low Intermediate	2-3
High Intermediate	4-5
High	6-8

Zhou Z et al. Blood 2014;123:837-842

## **APPENDIX 4 – DECLARATION OF HELSINKI**

The trial will be conducted in accordance with the recommendations for physicians involved in research on human Patients adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each subject's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the subject to refuse to participate in the trial without giving reasons must be respected.

### **WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**

#### **Ethical Principles for Medical Research Involving Human Subjects**

##### **A. INTRODUCTION**

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. 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."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

## **B. BASIC PRINCIPAL FOR ALL MEDICAL RESEARCH**

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. 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 on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the funder or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

## APPENDIX 5 – KNOWN STRONG IN VIVO INHIBITORS AND INDUCERS OF CYP3A4

Strong Inhibitors of CYP3A <sup>a</sup>	Strong Inducers of CYP3A <sup>e</sup>
boceprevir clarithromycin <sup>b</sup> conivaptin <sup>b</sup> grapefruit juice <sup>c</sup> itraconazole <sup>b</sup> ketoconazole <sup>b</sup> indinavir lopinavir/ritonavir <sup>b</sup> (combination drug) mibefradil <sup>d</sup> nefazodone nelfinavir posaconazole ritonavir <sup>b</sup> saquinavir telaprevir telithromycin voriconazole	carbamazepine <sup>f</sup> phenytoin <sup>f</sup> rifampin <sup>f</sup> St John's wort <sup>f</sup>

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by  $\geq 5$ -fold.

b. In vivo inhibitor of P-glycoprotein.

c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).

d. Withdrawn from the United States market because of safety reasons.

e. A strong inducer for CYP3A is defined as an inducer that results in  $\geq 80\%$  decrease in the AUC of a substrate for CYP3A.

f. In vivo inducer of P-glycoprotein.

**Note:** The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the SCTU

### Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo>

## APPENDIX 6 – SUMMARY OF RESPONSE CRITERIA

### 1) Overall Response Rate

Overall response rate is defined by objective response (partial or complete) in any of the patients as determined by the Lugano classification for NHL (Cheson 2014)<sup>28</sup>. The 2007 revised response criteria have been used with regard to bone marrow biopsy contribution to the response assessment (Cheson 2007)<sup>29</sup>.

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Relapsed and Progressive disease (PD)

### 2) PET-CT Response Assessment

- 3) See APPENDIX 7 to understand how “Overall Investigator Response Assessment” (overall time-point assessment) should be assessed and recorded at 12 month follow up and 24 month follow up.

Response and Site	PET-CT–Based Response	CT-Based Response
<b>Complete</b>	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3 <sup>+</sup> with or without a residual mass on 5PS <sup>†</sup>  It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi  No extralymphatic sites of disease
Non measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow. (If bone marrow involvement with high-grade lymphoma identified on biopsy at baseline and a complete metabolic response was achieved, but with no bone marrow biopsy assessment after treatment- the	Normal by morphology; if indeterminate, IHC negative. (If bone marrow involvement with high-grade lymphoma identified on biopsy at baseline and a complete radiologic response was achieved, but with no bone marrow biopsy assessment after

Response and Site	PET-CT–Based Response	CT-Based Response
	overall response should be classified as a partial response)	treatment- the overall response should be classified as a partial response)
<b>Partial</b>	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 <sup>1</sup> with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
<b>No response or stable disease</b>	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
<b>Progressive disease</b>	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:

Response and Site	PET-CT–Based Response	CT-Based Response
nodes/nodal masses		
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement



## APPENDIX 7- APPLYING LUGANO RESPONSE CLASSIFICATION TO CLINICAL TRIALS

Based on: [https://www.parexel.com/files/4514/5744/8554/Cheson\\_Lugano\\_whitepaper.pdf](https://www.parexel.com/files/4514/5744/8554/Cheson_Lugano_whitepaper.pdf)

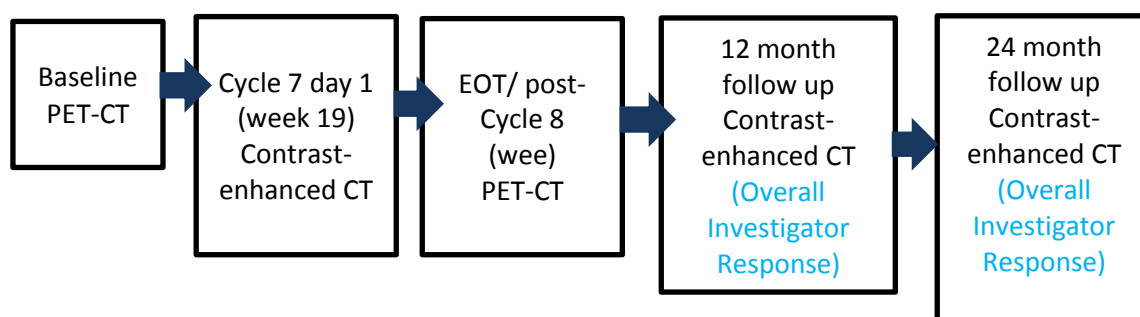
The guidance below is provided to assist sites to:

1. Understanding how to record response assessment based on imaging of differing modalities (PET-CT and CT) as part of the clinical trial.

The Southampton Clinical Trials Unit should be contacted to assist site investigators wherever necessary.

### Assessing response based on PET-CT and CT imaging<sup>92</sup>

To measure and monitor response as part of the clinical trial, in order to meet the clinical endpoints of the study, repeat imaging is performed at set time-points. At specific time-points PET-CT is the imaging modality of choice whilst at others CT alone is performed. The modalities have different criteria for responses as specified in the Lugano classification (Cheson 2014) see APPENDIX 6. These different criteria can result in contradictory responses between PET and CT. The overall investigator response assessment has been included in the ECRF and database to allow imaging results to be interpreted and incorporated. Below is some guidance on interpretation of imaging outcomes. If investigators are having difficulty understanding response to record in the ECRF, the Southampton Clinical Trials Unit should be contacted.



Overall Investigator Response Assessment will be recorded at the following timepoints (in addition to CT-based response):

1. 12 month follow up
2. 24 month follow up

To understand how the disease is behaving, it is important to take into account recent imaging when recording the overall investigator response assessment. The PET-CT provides information about remission status through FDG-avidity that the CT alone cannot provide.

GUIDING PRINCIPLE 1	GUIDING PRINCIPLE 2
FOR TIMEPOINTS WHEN FDG-PET IS AVAILABLE, THE FDG-PET ASSESSMENT TRUMPS THE CT RESPONSE	FOR TIMEPOINTS WHEN ONLY CT IS AVAILABLE, FOLLOWING A PRIOR FDG-PET ASSESSMENT, CT ASSESSMENTS MAY BE AFFECTED BY THE PRIOR PET/CT ASSESSMENT

For example, a complete metabolic response (CMR) by PET-CT may be recorded where there is no FDG-avid disease (score 1 or 2 on the 5 point scoring (5PS) system), despite the presence of residual volume disease (of for example 3cm). Subsequent CT imaging cannot benefit from the information that FDG-uptake provides. Therefore, residual disease (of for example 3cm) would be classed as a partial remission based on the Lugano classification. In fact, in this case, if there has been no progression in size by CT measurements, the overall investigator response assessment should record that the patient remains in complete response, unless there is other evidence of progressive disease. Other examples below may assist with entering overall investigator response:

Example:	PET assessment is consistent with CR and CT scan assessment is consistent with PR. A scan at subsequent timepoint CT still demonstrates PR. Thus the overall assessment, even in the absence of PET, is CR, until another PET assessment demonstrates otherwise or the CT scan worsens.
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Let's look at some examples:

In scenario A, the PR at Week 12 is based on CT without accompanying PET scan. At Week 24, the subsequent PET image supports CMR based on the change in score from 3 (assumed positive at baseline in this example) to a score of 1.

SCENARIO A	CT ASSESSMENT	PET-CT ASSESSMENT	COMBINED OVERALL TIMEPOINT ASSESSMENT
Baseline CT and PET	Select disease on CT	Score = 3	Not applicable
CT TP2 – Week 12	PR	No PET	PR
CT TP3 and PET – Week 24	CR	Score = 1	CMR/CR

In scenario C, the PET is positive at baseline with a score of 4. In this scenario, it is assumed that the protocol does not require scheduled PET until Week 24. At Week 24, a CT demonstrates PR but a PET score of 3 (changing from score of 4 at baseline) this may be consistent with PMR or CMR; If a score of 3 is considered positive by PET per protocol this remains PMR even if the subsequent CT suggest a CR. A subsequent PET is recommended to clarify the subject's response status. If a score of 3 is considered negative by PET per protocol, a subsequent PET is not necessary.

SCENARIO C	CT ASSESSMENT	PET-CT ASSESSMENT	OVERALL TIMEPOINT ASSESSMENT
Baseline CT and PET	Select Disease on CT	Score = 4	Not applicable
CT TP2 – Week 12	SD	No PET	SD
CT TP3 and PET – Week 24	PR	Score = 3	PMR/PR or CMR/CR
CT TP4 – Week 36	CR	No PET	PMR/PR or CMR/CR

In scenario B, the PET is considered positive at baseline with a score of 3, 4 or 5. While PR is met on CT, the PET score of 2 at Week 12 is consistent with a CMR. The subsequent PR on CT at Week 24, does not preclude an overall CMR even in the absence of PET, provided there is no worsening on CT between Week 12 and Week 24.

SCENARIO B	CT ASSESSMENT	PET-CT ASSESSMENT	COMBINED OVERALL TIMEPOINT ASSESSMENT
Baseline CT and PET	Select disease on CT	Score = 3, 4 or 5	Not applicable
CT TP2 and PET – Week 12	PR (Residual extranodal disease present)	Score = 2	CMR/CR
CT TP3 – Week 24	PR (Residual extranodal disease present)	No PET	CMR/CR

In scenario D, the PET is positive at baseline with a score of 4. At Week 12, a CT demonstrates PR but a PET score of 3 (changing from score of 4 at baseline) may be consistent with PMR or CMR as in scenario C. At Week 24, the CT demonstrates progression but no PET is acquired to verify the progression on CT. Investigator overall response should be interpreted as indeterminate response (IR), if the patient is receiving atezolizumab. See indeterminate response section below

SCENARIO D	CT ASSESSMENT	PET-CT ASSESSMENT	OVERALL TIMEPOINT ASSESSMENT
Baseline CT and PET	Select Disease on CT	Score = 4	Not applicable
CT TP2 and PET – Week 12	PR	Score = 3	PMR/PR or CMR/CR
CT TP3 – Week 24	PD	No PET	IR

## APPENDIX 8 – PROTON PUMP INHIBITORS

Proton pump inhibitors
omeprazole esomeprazole lansoprazole dexlansoprazole rabeprazole pantoprazole

## 20 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V3, 01/Nov/2017	<ul style="list-style-type: none"> <li>- SCHEDULE OF OBSERVATIONS AND PROCEDURES updated to allow ECOG and physical exams to be performed within 24 hours of day1 of each cycle.</li> <li>- Inclusion and exclusion criteria updated to clarify requirements for tumour block, cardiac function and treatment with proton pump inhibitors.</li> <li>- 6.1 TREATMENT SCHEDULE updated to clarify that acalabrutinib can be administered prior to R-CHOP on day 1 of each cycle.</li> <li>- 7.3 TRANSLATIONAL RESEARCH – clarification on hierarchy of testing for tumour block</li> <li>- ISRCTN reference number added to the front of the protocol.</li> <li>- RSI table updated with current editions of Investigator Brochures</li> <li>- 13.3 SAFETY REVIEW COMMITTEE (SRC) clarification on patient requirement for SRC to take place.</li> <li>- APPENDIX 8 added to list prohibited proton pump inhibitors.</li> </ul>
V4, 23/May/2018	<ul style="list-style-type: none"> <li>- - List of abbreviations – addition of Pneumocystis jirovecii pneumonia (PCP)</li> <li>- - Schedule of Observations and Procedures amended to clarify PET-CT requirements, introduce Tissue Block Screening consent prior to main study consent, introduce 48 hour window to complete Electrocardiogram and Echocardiogram and introduce window for Week 19 and EoT CT Scan.</li> <li>- Study Design amended to confirm DLT reporting period.</li> <li>- Selection and Enrolment of Participants amended to introduce a centralised review of signed consent forms at the SCTU via nhs.net email.</li> <li>- Exclusion Criteria amended to clarify that all women and men who can bear children must agree to use highly effective forms of contraception.</li> <li>- Registration/Randomisation Procedures amended to introduce Tissue Block Screening consent form prior to main study consent.</li> <li>- Screening Procedures amendment to clarify PET-CT requirements and amended to introduce Tissue Block Screening consent prior to main study consent.</li> <li>- Trial Procedures amended to introduce +/- 1 week window for Week 19 CT Scan and EoT PET-CT window</li> <li>- Follow Up amended to include survival follow-up visit time points.</li> <li>- Supportive Care amended to include PCP prophylaxis and clarification on timing for H2 receptor antagonist treatment.</li> <li>- Additional Treatment for DLBCL updated to include PCP prophylaxis</li> <li>- Safety – Expectedness amended in line with updated reference safety information.</li> <li>- Update to sections referencing the Data Protection Act. Wording changed to “current Data Protection Regulations” in line with GDPR.</li> </ul>

V5, 08/Nov/2018	<ul style="list-style-type: none"> <li>- Inclusion criteria updated to exclude patients 65 and over</li> <li>- Rationale and risk benefit for current trial – updated to provide rationale for urgent safety measure changes</li> <li>- Supportive Care – updated to introduce infective prophylaxis for patients aged 65 and over.</li> </ul>
V6, 15/Jul/2019	<ul style="list-style-type: none"> <li>- BTK occupancy sub-study removed.</li> <li>- Discrepancies between text and schedule of observations corrected for baseline blood tests.</li> <li>- Adverse Events to be collected from date of consent.</li> <li>- Permitted window introduced for End of Treatment and Follow-up visits.</li> <li>- Permitted time window introduced for translational samples.</li> <li>- Clarification added that bi-dimensional measurements are expected for CT scans.</li> <li>- PHOENIX study findings included in the Rationale and Risk Benefits for Current Trial.</li> <li>- Inclusion criteria updated to permit patient 16 years and above.</li> <li>- Exclusion criteria updated to state patients taking a proton pump inhibitor should be switched to a short-acting H2-receptor antagonist or antacid prior to study entry.</li> <li>- Supportive care updated to state GCSF support and antimicrobial prophylaxis against PCP is mandatory.</li> <li>- Reference Safety Information updated.</li> <li>- Clarifications and a definition of WOCBP added to the contraception section.</li> <li>- Definition and reporting requirements for overdose updated.</li> <li>- Warnings and Precautions for acalabrutinib use added.</li> <li>- Guidance added around ciprofloxacin use.</li> <li>- Haematological toxicity guidance updates.</li> <li>- Reporting requirements added for drug induced liver injury and suspected transmission of infectious agents.</li> <li>- Clarifications added to pregnancy follow-up and reporting requirements.</li> <li>- Data sharing statement added.</li> </ul>