Cancer Research UK & UCL Cancer Trials Centre
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website: http://www.ctc.ucl.ac.uk/

Director: Professor JA Ledermann

Medicines & Healthcare products Regulatory Agency
10 South Colonnade
Canary Wharf
London
E14 4PU

28/May/2020

Dear Sir/Madam,

Trial Title: A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma, fit for autologous stem cell transplant, who fail to reach complete metabolic remission after first or second line salvage therapy

Funders: Bristol-Myers Squibb
Sponsor Name: University College London
Sponsor's Trial ID Number: UCL/15/0515
EudraCT Number: 2017-002544-32

Amendment Number/Date: 6 – Protocol v4.0, 28/May/2020

Please find enclosed a Notification of Substantial Amendment Form and associated documents for the ANIMATE trial.

The following documents are provided:

		Version	Date
1.	Notice of Substantial Amendment form	N/A	N/A
2.	Protocol (with tracked changes)	v4.0	28.05.2020
3.	Protocol (final clean copy)	v4.0	28.05.2020
4.	Reference Safety Information – Nivolumab Investigator Brochure	v18	25.06.2019
5.	PO number/receipt for payment	N/A	N/A

Protocol Amendment Details

This amendment will change the version number of the protocol from 3.0 to 4.0; tracked and clean copies of the amended protocol have been submitted.

The main changes from protocol v3.0 are listed in the table below:

Protocol Section (no./title)	Summary of main changes from previous version.
TMG page 1	Amendment to Dr Beth Phillips' job title and location. Addition of new Trial Coordinator

Protocol Section (no./title)	Summary of main changes from previous version.
4.2.2 Required documentation	Removal of 'Clinical Trial Site Agreement' as the trial uses the model Non-commercial agreement
8.2 Treatment Summary	Clarification that PET-CT scans should be conducted 'during' cycle 4
8.4 Treatment discontinuation criteria	Added back in G4 lipase abnormalities, as lipase testing has been added back into assessments.
8.5.1 Autoimmune complications	Removal of wording 'summary of product characteristics' and replaced with 'relevant appendix within the Investigator Brochure'
8.5.1.8 Management of myocarditis	Addition of section to manage myocarditis. Current Investigator Brochure v18 has new guidance for managing myocarditis. Section created based on information within IB.
8.5.1.9 Management of other immune-related adverse reactions	Removal of wording 'summary of product characteristics' and replaced with 'relevant appendix within the Investigator Brochure' Removed reference to myocarditis as this now has a separate standalone section for toxicity management
9.2 Assessment of eligibility for nivolumab treatment	• Clarification added for timing of eligibility assessment; 'Once registered on trial and after completion of…' • Added confirmation that the PET-CT scan is to include neck, chest, abdomen and pelvis. • Added clarification to stipulate the ceCT scan areas; neck, chest, abdomen and pelvis (NCAP). • Added in details to inform sites to contact UCL CTC if the timeframe of assessments is outside those stipulated. • Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. • Hep C testing; amended from 'Hepatitis C DNA' & 'HCV DNA' to 'Hepatitis C RNA' & 'HCV RNA'. DNA wording used in error, Hep C is a RNA virus.
9.3 Assessments prior to cycle 1of Nivolumab	• Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests.
9.4 Assessments during nivolumab treatment	• Clarification added to heading; 'Assessments during **Nivolumab** Treatment'. • Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. • ceCT4 scan times have been added to reflect the fact that these should be in keeping with the timings of the PET4 scan. • Various minor re-wording to provide clarity of assessment timing.
9.5 Assessments on completion of nivolumab treatment	• Clarification added to heading; 'Assessments during **Nivolumab** Treatment'. • Added details of the CT guided biopsy, which was previously missed • Added in wording to provide clarification that the ceCT scan should be conducted as well as PET-CT; 'Contract enhanced CT scan to be carried out at least 11-13 days after last trial treatment administration, and sent to the PET core lab for central review. This should be performed at the same imaging session as the PET-CT if feasible. If performed at the same session, the ceCT scan should be performed after the low dose PET-CT (see trial Imaging Manual and Sample Tracking Website Manual for details).'
9.6.2 Patients who receive nivolumab	Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests.

Protocol Section (no./title)	Summary of main changes from previous version.
9.7 Assessments at time of disease progression	Added details of the CT guided biopsy, which was previously missed
11.3 Timelines for Data Return	Reference to section 14.2 has been amended to reflect the renamed title; 'For Cause On-Site Monitoring' has been renamed 'Triggered On-Site Monitoring'
12.4.1 Autoimmune events due to nivolumab	Duplication of paragraph, 'The following adverse events of special interest for Nivolumab must be reported on the appropriate AE of Special Interest form within **24 hours of confirmed diagnosis'** therefore removed
14.1 Centralised Monitoring	Reference to section 14.2 has been amended to reflect the renamed title; 'For Cause On-Site Monitoring' has been renamed 'Triggered On-Site Monitoring'
14.2 For Cause On-Site Monitoring	Section renamed. Was 'For Cause On-Site Monitoring' now reads 'Triggered On-Site Monitoring'
15 Withdrawal of patients	New paragraph added 15.1 – 'Patients who do not start treatment' There are now 6 sub-sections to section 15
16.4 Withdrawal from Trial Participation by a Site	Removal of 'CTSA' and replaced with 'site agreement (mNCA)' to reflect the correct type of contract used within the trial
19 Ethical and Regulatory considerations	Data protection Act updated from 1998 to 2018 to reflect the new update. And addition of the General Data Protection Regulation (EU)2016/679 (GDPR) (*changes previously missed in error from v2.1 protocol amendment*)
19.5 Patient Confidentiality & Data Protection	DP Act date updated to 2018, and addition of GDPR.
21 Funding	Removal of 'CTSA' and replaced with 'site agreement (mNCA)' to reflect the correct type of contract used within the trial
Appendix 1 Abbreviations	Addition of the following: GDPR - General Data Protection Regulation mNCA - Model Non-Commercial Agreement
Appendix 2.1 tables 'Patients who receive nivolumab' footnote 4 & 'Investigations during treatment' footnote 2	Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. Hep C testing; amended from ''HCV DNA' to 'HCV RNA'. DNA wording used in error, Hep C is a RNA virus.
Appendix 2.2 table 'Patients who do not receive nivolumab' footnote 4	Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. Hep C testing; amended from 'HCV DNA' to 'HCV RNA'. DNA wording used in error, Hep C is a RNA virus.

Other minor clarifications have been made to the protocol, as well as general administrative and typographical edits. Please see tracked changes version for full details.

Nivolumab

Current RSI: Nivolumab Investigator Brochure, version 16, section 5.6, table 5.6.1-1, date of release 23/Jun/2017
Proposed RSI: Nivolumab Investigator Brochure, version 18, appendix 1, table 1-1, date of release 25/Jun/2019
Reason for change: significant changes to RSI section of IB
PIS: The Patient Information Sheet has been updated and is included in this submission.
Benefit-risk statement: The benefit-risk profile of the Nivolumab has changed, however it remains favourable following the risk mitigation measures introduced in the protocol.

Implementation Guidance:
Following approval, the new RSI will be implemented immediately
The Sponsor requests to implement the proposed documents as RSI for the trial upon MHRA approval. The DSUR for the trial has been submitted on 24/Apr/2020 for the reporting period of 27/Feb/2019 to 26/Feb/2020.

New Sites

There will be 5 new sites participating in the trial:

- United Lincolnshire Hospitals NHS Trust (**Lincoln County Hospital, PI Dr Gamal Sidra**)
- University Hospitals Plymouth NHS Trust (**Derriford Hospital, PI Dr Patrick Medd**)
- Sandwell and West Birmingham Hospitals NHS Trust (**Sandwell General Hospital, PI Dr Syeda Yasmin Hasan**)
- Clatterbridge Cancer Centre NHS Foundation Trust (**Clatterbridge Cancer Centre,** based at Royal Liverpool Hospital, **PI Dr Nagesh Kalakonda**)
- NHS Grampian (**Aberdeen Royal Infirmary, PI Dr Dominic Culligan**)

Change in Principal Investigators

The Principal Investigators have changed at the following sites:

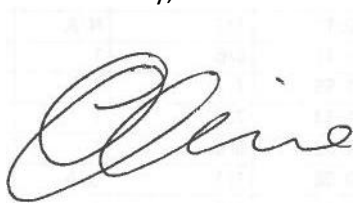
- The Christie NHS Foundation Trust (**The Christie Hospital**), was Dr Kim Linton and **transferring to Dr Elizabeth (Beth) Phillips**
- Nottingham University Hospital NHS Trust (**Nottingham University Hospital**), was Dr Andrew McMillan and **transferring to Dr Nicolas Martinez-Calle**

Payment Details

Please send an invoice for £250 for this amendment to apinvoices@ucl.ac.uk and ctc.animate@ucl.ac.uk, quoting PO number H01-3054587.

If you have any questions, please do not hesitate to contact me.

Yours faithfully,



Mrs Emma Lawrie
ANIMATE Trial Coordinator

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