The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

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Head of Division/Head of Stroke
Stroke Association Professor of Stroke Medicine:
**Professor P M W Bath**

11 March 2014

Information Processing Unit
Area 6, MHRA
151 Buckingham Palace Road
Victoria
London
SW1W 9SZ

| | |
|---|---|
| Eudract Number: | 2007-006749-42 |
| Substantial amendment reference: | SA/03/14 |
| Protocol No: | 31350 & 08093 V1.4 Protocol 26/02/2013 |

Dear Sir or Madam

**Trial Title: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke**

Please find enclosed a substantial amendment for the above trial to update the protocol. We look forward to receiving your approval letter.

We look forward to receiving your acknowledgement and approval.

Yours faithfully

Sally Utton
TARDIS Trial Manager

Encs: CD with Notice of Substantial amendment form
Protocol, clean and track changes version
Change document from v1.4 to v1.5

cc: RGS, University of Nottingham

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**Professor P M W Bath**

11 March 2014

Dr L A Ruben
Chair of South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

| | |
|---|---|
| Your reference: | 08/H1102/112 |
| Substantial amendment reference: | SA/03/14 |
| Eudract Number: | 2007-006749-42 |
| Protocol No: | 31350 & 08093 V1.4 Protocol 26/02/2013 |

Dear Dr Ruben and colleagues

**Trial Title: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke**

Please find enclosed a substantial amendment for the above trial to update the protocol. We look forward to receiving your approval letter.

Yours sincerely

Sally Utton
TARDIS Trial Manager

Encs: Notice of Substantial amendment form
Protocol, clean and track changes version
Change document from v1.4 to v1.5

cc: RGS, University of Nottingham

**Substantial Amendment Notification Form (Cf. Section 3.7.b of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])**

**NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION**

*For official use:*

| | |
|---|---|
| Date of receiving the request : | Grounds for non acceptance/ negative opinion : ❑<br>Date : |
| Date of start of procedure: | Authorisation/ positive opinion : ❑<br>Date : |
| Competent authority registration number of the trial:<br>Ethics committee registration number of the trial : | Withdrawal of amendment application ❑<br>Date : |

*To be filled in by the applicant:*

This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

## A TYPE OF NOTIFICATION

| | |
|---|---|
| **A.1 Member State in which the substantial amendment is being submitted:** | **UK** |
| **A.2 Notification for authorisation to the competent authority:** | **❑ yes** |
| **A.3 Notification for an opinion to the ethics committee:** | **❑ yes** |

## B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

**B.1 Does the substantial amendment concern several trials involving the same IMP?**[2] **❑ no**

B.1.1 If yes repeat this section as necessary.

**B.2 Eudract number: 2007-006749-42**

**B.3 Full title of the trial** : Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack (TIA): a randomised controlled trial

**Sponsor's protocol code number, version, and date: 31350 and 08093 TARDIS Protocol V1.4 26/02/13**

## C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

| **C.1** | **Sponsor** |
|---|---|
| C.1.1 | Organisation: University of Nottingham |
| C.1.2 | Name of person to contact: Mr Paul Cartledge |
| C.1.3 | Address : Head of Research Grants and Contracts, University of Nottingham, Research Innovation Services, King's Meadow Campus, Lenton Lane, Nottingham NG7 2NR |
| C.1.4 | Telephone number : 0115 951 5679 |
| C.1.5 | Fax number : 0115 951 3633 |
| C.1.6 | e-mail: paul.cartledge@nottingham.ac.uk |

| **C.2** | **Legal representative**[3] **of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)** |
|---|---|
| C.2.1 | Organisation: |
| C.2.2 | Name of person to contact: |
| C.2.3 | Address : |
| C.2.4 | Telephone number : |
| C.2.5 | Fax number : |

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

2 Cf. Section 3.7. of the detailed guidance CT-1.

3 As stated in Article 19 of Directive 2001/20/EC.

| | |
|---|---|
| C.2.6 | e-mail: |

## D APPLICANT IDENTIFICATION (please tick the appropriate box)

| D.1 | Request for the competent authority | |
|---|---|---|
| D.1.1 | Sponsor | No |
| D.1.2 | Legal representative of the sponsor | ❑ |
| D.1.3 | Person or organisation authorised by the sponsor to make the application. | No |
| D.1.4 | Complete below: | |
| D.1.4.1 | Organisation : University of Nottingham | |
| D.1.4.2 | Name of person to contact : Sally Utton | |
| D.1.4.3 | Address : Division of Stroke, Clinical Sciences Building, City Hospital Campus, Hucknall Road, Nottingham NG5 1PB | |
| D.1.4.4 | Telephone number : 0115 823 0287 | |
| D.1.4.5 | Fax number : 0115 823 1771 | |
| D.1.4.6 | E-mail Sally.utton@nottingham.ac.uk | |

| D.2 | Request for the Ethics Committee | |
|---|---|---|
| D.2.1 | Sponsor | **YES** |
| D.2.2 | Legal representative of the sponsor | ❑ |
| D.2.3 | Person or organisation authorised by the sponsor to make the application. | **YES** |
| D.2.4 | Investigator in charge of the application if applicable[4]: | |
| | • Co-ordinating investigator (for multicentre trial) | **YES** |
| | • Principal investigator (for single centre trial): | ❑ |
| D.2.5 | Complete below | |
| D.2.5.1 | Organisation : University of Nottingham | |
| D.2.5.2 | Name : Mrs Sally Utton | |
| D.2.5.3 | Address : Clinical Sciences Building, Div of Clinical Neuroscience, Stroke, c/o Nottingham City Hospital, Hucknall Rd, Notitngham NG5 1PB | |
| D.2.5.4 | Telephone number : 0115 823 0287 | |
| D.2.5.5 | Fax number : 0115 823 1771 | |
| D.2.6 | E-mail : sally.utton@nottingham.ac.uk | |

## E SUBSTANTIAL AMENDMENT IDENTIFICATION

| E.1 | **Sponsor's substantial amendment code number, version, date for the clinical trial concerned: (SA03/14)** |
|---|---|

| E.2 | Type of substantial amendment | |
|---|---|---|
| E.2.1 | **Amendment to information in the CT application form** | **no** |
| E.2.2 | **Amendment to the protocol** | no ❑ |
| E.2.3 | **Amendment to other documents appended to the initial application form** | no ❑ |
| E.2.3.1 | If yes specify: | |
| E.2.4 | **Amendment to other documents or information:** | no ❑ |
| E.2.4.1 | If yes specify: | |
| E.2.5 | **This amendment concerns mainly urgent safety measures already implemented[5]** | no ❑ |
| E.2.6 | **This amendment is to notify a temporary halt of the trial[6]** | no ❑ |
| E.2.7 | **This amendment is to request the restart of the trial[7]** | no ❑ |

4 According to national legislation.
5 Cf. Section 3.9. of the detailed guidance CT-1.
6 Cf. Section 3.10. of the detailed guidance CT-1.
7 Cf. Section 3.10. of the detailed guidance CT-1.

| E.3 | Reasons for the substantial amendment: | |
|---|---|---|
| E.3.1 | **Changes in safety or integrity of trial subjects** | **no** ❑ |
| E.3.2 | **Changes in interpretation of scientific documents/value of the trial** | **no** ❑ |
| E.3.3 | **Changes in quality of IMP(s)** | **no** ❑ |
| E.3.4 | **Changes in conduct or management of the trial** | **no** ❑ |
| E.3.5 | **Change or addition of principal investigator(s), co-ordinating investigator** | **no** ❑ |
| E.3.6 | **Change/addition of site(s)** | **no** ❑ |
| E.3.7 | **Other change** | **yes** ❑ |
| E.3.7.1 | **If yes, specify:** Update of protocol to v1.5 28/02/14. | |

| E.4 | Information on temporary halt of trial[8] N/A | |
|---|---|---|
| E.4.1 | **Date of temporary halt** (YYYY/MM/DD) | |
| E.4.2 | **Recruitment has been stopped** | no ❑ |
| E.4.3 | **Treatment has been stopped** | no ❑ |
| E.4.4 | Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment ( ) | |
| E.4.5 | **Briefly describe (free text):**<br>• Justification for a temporary halt of the trial<br>• The proposed management of patients receiving treatment at time of the halt *(free text)*.<br>The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text)*. | |

## F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9] *(free text)*:

| Previous and new wording in track change modus | New wording | Comments/explanation/reasons for substantial amendment |
|---|---|---|
| Updated protocol to v1.5. | See track changes on protocol and detailed change document enclosed. | Changes have been made to expand the inclusion criteria to include MR diffusion imaging, update dosing to include ranges, remove room temperature definitions, include posteria fossa events, remove reference to TCD, add protocol violations. Detailed changes document and track changes version of the protocol is enclosed. |

[8] Cf. Section 3.10. of the detailed guidance CT-1.

[9] Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

## G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

**G.1 Type of change**

G.1.1 **Addition of a new site**
G.1.1.1 **Principal investigator** (provide details below)
**G.1.1.1.1** Given name
G.1.1.1.2 Middle name (if applicable)
**G.1.1.1.3** Family name
G.1.1.1.4 Qualifications (MD……..) MD
Professional address:
G.1.2 **Addition of a new site**
G.1.2.1 **Principal investigator** (provide details below)
**G.1.2.1.1** Given name
G.1.2.1.2 Middle name (if applicable)
**G.1.2.1.3** Family name
G.1.2.1.4 Qualifications (MD……..) MD
Professional address:

G.1.3 **Addition of a new site**
G.1.3.1 **Principal investigator** (provide details below)
**G.1.3.1.1** Given name
G.1.3.1.2 Middle name (if applicable)
**G.1.3.1.3** Family name
G.1.3.1.4 Qualifications (MD……..) MD
Professional address:

G.1.4 **Addition of a new site**
G.1.4.1 **Principal investigator** (provide details below)
**G.1.4.1.1** Given name
G.1.4.1.2 Middle name (if applicable)
**G.1.4.1.3** Family name
G.1.4.1.4 Qualifications (MD……..) MD
Professional address

G.1.5 **Addition of a new site**
G.1.5.1 **Principal investigator** (provide details below)
**G.1.5.1.1** Given name
G.1.5.1.2 Middle name (if applicable)
**G.1.5.1.3** Family name
G.1.5.1.4 Qualifications (MD……..) MD
Professional address:

G.1.6 **Removal of an existing site**
G.1.6.1 **Principal investigator** (provide details below)
**G.1.6.1.1** Given name
G.1.6.1.2 Middle name (if applicable)
**G.1.6.1.3** Family name
**G.1.6.1.4** Qualifications (MD……..) MD
G.1.6.1.5 Professional address
G.1.6.1.6
G.1.7 **Change of co-ordinating investigator** (provide details below of the new coordinating investigator)
G.1.7.1 Given name
G.1.7.2 Middle name
G.1.7.3 Family name
G.1.7.4 Qualification (MD…….)
Professional address
G.1.7.5 Indicate the name of the previous co-ordinating investigator:

G.1.8 **Change of principal investigator at an existing site** (provide details below of the new principal

investigator)
G.1.8.1 Given name
G.1.8.2 Middle name
G.1.8.3 Family name
G.1.8.4 Qualification (MD……)
G.1.8.5 Professional address: Indicate the name of the previous co-ordinating investigator:

G.1.9 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)
G.1.9.1 Given name
G.1.9.2 Middle name
G.1.9.3 Family name
G.1.9.4 Qualification (MD……)
G.1.9.5 Professional address: Indicate the name of the previous co-ordinating investigator:

## H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

| | |
|---|---|
| **H.1 Change of e-mail contact for feedback on application*** | |
| **H.2** Change to request to receive an .xml copy of CTA data | ❑ no |
| H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? | ❑ no |
| H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses): | |
| H.2.2 Do you want to receive this via password protected link(s)[10]? | ❑ yes ❑ no |
| If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s) | |
| H.2.3 Do you want to stop messages to an email for which they were previously requested? | ❑ yes ❑ no |
| H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent: | |
| **(*This will only come into effect from the time at which the request is processed in EudraCT).** | |

## I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

*Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).*

| | |
|---|---|
| **I.1 Cover letter** | **YES** |
| **I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)** | ❑ |
| **I.3 Entire new version of the document[11]** | ❑ **Yes** |
| **I.4 Supporting information** | ❑ **Yes** |
| **I.5 Revised .xml file and copy of initial application form with amended data highlighted** | **no** |
| **I.6 Comments on any novel aspect of the amendment if any** | |

## J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

**J.1** I hereby confirm on behalf of the sponsor that
- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

---

[10] This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)

[11] Cf. Section 3.7.c. of the detailed guidance CT-1.

| J.2 | **APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY**(as stated in section D.1): | |
|---|---|---|
| J.2.1 | Signature [12]: | Philip Batt |
| J.2.2 | Print name : | PHILIP BATT |
| J.2.3 | Date : | 14/3/14 |

| J.3 | **APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE** (as stated in section D.2): | |
|---|---|---|
| J.3.1 | Signature [13]: | Philip Batt |
| J.3.2 | Print name: | PHILIP BATT |
| J.3.3 | Date : | 14/3/14 |

[12] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
[13] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.