

**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*<sup>1</sup>)**

**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 : <input type="checkbox"/>
	Date :
Date of start of procedure:	Authorisation/ positive opinion : <input type="checkbox"/>
	Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application <input type="checkbox"/>
	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**

<b>A.1 Member State in which the substantial amendment is being submitted:</b>	Netherlands
<b>A.2 Notification for authorisation to the competent authority:</b>	<input checked="" type="checkbox"/>
<b>A.3 Notification for an opinion to the ethics committee:</b>	<input type="checkbox"/>

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

<b>B.1 Does the substantial amendment concern several trials involving the same IMP?<sup>2</sup></b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
B.1.1 If yes repeat this section as necessary.	

**B.2 Eudract number:** 2016-002976-28

**B.3 Full title of the trial:**

A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of CNP520 in participants at risk for the onset of clinical symptoms of Alzheimer's Disease (AD).

**B.4 Sponsor's protocol code number, version, and date:** CCNP520A2202J, Version 03, dated 07-Jan-2020

**C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST**

<b>C.1 Sponsor</b>	
C.1.1 Organisation:	Novartis Pharma AG
C.1.2 Name of person to contact:	5.1.2.e
C.1.3 Address :	Lichtstrasse 35, 4056 Basel, Switzerland
C.1.4 Telephone number :	+41 5.1.2.e
C.1.5 Fax number :	
C.1.6 e-mail:	5.1.2.e @novartis.com

**C.2 Legal representative<sup>3</sup> of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)**

C.2.1 Organisation:	Novartis Pharma Arzneimittel GmbH
C.2.2 Name of person to contact:	5.1.2.e
C.2.3 Address :	Roonstrasse 25, 90429 Nuernberg, Germany
C.2.4 Telephone number :	+49 5.1.2.e
C.2.5 Fax number :	+49 5.1.2.e
C.2.6 e-mail:	5.1.2.e @novartis.com

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

<b>D.1 Request for the competent authority</b>
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<sup>1</sup> OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

<sup>2</sup> Cf. Section 3.7. of the detailed guidance CT-1.

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

D.1.1	Sponsor	<input type="checkbox"/>
D.1.2	Legal representative of the sponsor	<input type="checkbox"/>
D.1.3	Person or organisation authorised by the sponsor to make the application.	<input checked="" type="checkbox"/>
D.1.4	Complete below:	
D.1.4.1	Organisation: Parexel International Romania S.R.L.	
D.1.4.2	Name of person to contact : 5.1.2.e	
D.1.4.3	Address : Metropolis Center, Str. Grigore Alexandrescu, No. 89-97, Bucharest, 010624, Romania	
D.1.4.4	Telephone number : +40 5.1.2.e	
D.1.4.5	Fax number : +40 5.1.2.e	
D.1.4.6	E-mail: 5.1.2.e @Novartis.com	

<b>D.2 Request for the Ethics Committee</b>		
D.2.1	Sponsor	<input type="checkbox"/>
D.2.2	Legal representative of the sponsor	<input type="checkbox"/>
D.2.3	Person or organisation authorised by the sponsor to make the application.	<input type="checkbox"/>
D.2.4	Investigator in charge of the application if applicable <sup>4</sup> :	
	• Co-ordinating investigator (for multicentre trial)	<input type="checkbox"/>
	• Principal investigator (for single centre trial):	<input type="checkbox"/>
D.2.5	Complete below	
D.2.5.1	Organisation :	
D.2.5.2	Name :	
D.2.5.3	Address :	
D.2.5.4	Telephone number :	
D.2.5.5	Fax number :	
D.2.6	E-mail :	

## E SUBSTANTIAL AMENDMENT IDENTIFICATION

<b>E.1</b>	<b>Sponsor's substantial amendment code number, version, date for the clinical trial concerned: -</b> CCNP520A2202J, Protocol version 03, dated 07-Jan-2020; CNP520 Investigator's Brochure, Ed.6 dated 23-Aug-2019.
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<b>E.2</b>	<b>Type of substantial amendment</b>	
E.2.1	<b>Amendment to information in the CT application form</b>	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.2.2	<b>Amendment to the protocol</b>	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.2.3	<b>Amendment to other documents appended to the initial application form</b>	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.2.3.1	If yes specify: CNP520 Investigator's Brochure, Ed.6	
E.2.4	<b>Amendment to other documents or information:</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.4.1	If yes specify:	
E.2.5	<b>This amendment concerns mainly urgent safety measures already implemented<sup>5</sup></b>	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.2.6	<b>This amendment is to notify a temporary halt of the trial<sup>6</sup></b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.7	<b>This amendment is to request the restart of the trial<sup>7</sup></b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>

<sup>4</sup> According to national legislation.

<sup>5</sup> Cf. Section 3.9. of the detailed guidance CT-1.

<sup>6</sup> Cf. Section 3.10. of the detailed guidance CT-1.

<sup>7</sup> Cf. Section 3.10. of the detailed guidance CT-1.

<b>E.3</b>	<b>Reasons for the substantial amendment:</b>	
E.3.1	<b>Changes in safety or integrity of trial subjects</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.2	<b>Changes in interpretation of scientific documents/value of the trial</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.3	<b>Changes in quality of IMP(s)</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.4	<b>Changes in conduct or management of the trial</b>	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.3.5	<b>Change or addition of principal investigator(s), co-ordinating investigator</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.6	<b>Change/addition of site(s)</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.7	<b>Other change</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.7.1	<b>If yes, specify:</b>	
E.3.8	<b>Other case</b>	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.8.1	<b>If yes, specify</b>	

<b>E.4</b>	<b>Information on temporary halt of trial<sup>8</sup></b>
E.4.1	<b>Date of temporary halt</b>
E.4.2	Recruitment has been stopped <span style="float: right;">yes <input type="checkbox"/> no <input type="checkbox"/></span>
E.4.3	<b>Treatment has been stopped</b> <span style="float: right;">yes <input type="checkbox"/> no <input type="checkbox"/></span>
E.4.4	Number of patients in the follow-up period (after the treatment discontinuation) at time protocol amendment submission in the MS concerned:
E.4.5	<b>Briefly describe (free text):</b>
	<ul style="list-style-type: none"> <li>• <b>Justification for a temporary halt of the trial</b></li>   <li>• <b>The proposed management of patients receiving treatment at time of the halt (free text).</b></li> </ul> <p><b>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).</b></p>

**F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT<sup>9</sup> (free text):**

<b>Previous and new wording in track change modus</b>	<b>New wording</b>	<b>Comments/explanation/reasons for substantial amendment</b>
As described in the tracked changes version of the protocol v3.0, dated 07-Jan-2020, available upon request.	As described in the clean version of the protocol v3.0, dated 07-Jan-2020, available upon request.	The changes described in this protocol amendment were previously communicated to the HAs as part of the Urgent Safety Measure (USM) issued on 11-Jul-2019 and were included in the Follow-up #1 dated 15-July-2019, Notification to Investigators dated 05-Aug-2019 and Follow-up #2 Notification to Investigators dated 13- Dec 2019.

**CNP520 annual IB update:** The information in the updated IB describes recent non-clinical and clinical trial information in the field of Alzheimer’s prevention and treatment and added information about urgent safety measure (USM) for stopping assessment of CNP520 in the ongoing clinical studies. The updated IB is available upon request.

<sup>8</sup> Cf. Section 3.10. of the detailed guidance CT-1.

<sup>9</sup> 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**

<b>G.1 Type of change</b>
<b>G.1.1 Addition of a new site</b>
G.1.1.1 <b>Principal investigator</b> (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.....)
G.1.1.1.5 Professional address
<b>G.1.2 Removal of an existing site</b>
G.1.2.1 <b>Principal investigator</b> (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.....)
G.1.2.1.5 Professional address
<b>G.1.3 Change of co-ordinating investigator</b> (provide details below of the new coordinating investigator)
G.1.3.1 Given name
G.1.3.2 Middle name
G.1.3.3 Family name
G.1.3.4 Qualification (MD.....)
G.1.3.5 Professional address
G.1.3.6 Indicate the name of the previous co-ordinating investigator:
<b>G.1.4 Change of principal investigator at an existing site</b> (provide details below of the new principal investigator)
G.1.4.1 Given name
G.1.4.2 Middle name
G.1.4.3 Family name
G.1.4.4 Qualifications (MD.....)
G.1.4.5 Professional address
G.1.4.6 Indicate the name of the previous principal investigator:

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

<b>H.1 Change of e-mail contact for feedback on application*</b>
<b>H.2</b> Change to request to receive an .xml copy of CTA data <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>
H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>
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) <sup>10</sup> ? <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>
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? <span style="float: right;"><input type="checkbox"/> yes <input type="checkbox"/> no</span>
H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:
<b>(*This will only come into effect from the time at which the request is processed in EudraCT).</b>

**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).*

<b>I.1 Cover letter</b>	<input checked="" type="checkbox"/>
<b>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)</b>	<input type="checkbox"/>

<sup>10</sup> This requires a EudraLink account. (See <https://eudract.ema.europa.eu/> for details)

<b>I.3 Entire new version of the document<sup>11</sup></b>	EC <input checked="" type="checkbox"/> CA <input type="checkbox"/>
<b>I.4 Supporting information</b>	EC <input checked="" type="checkbox"/> CA <input type="checkbox"/>
<b>I.5 Revised .xml file and copy of initial application form with amended data highlighted</b>	<input checked="" type="checkbox"/>
<b>I.6 Comments on any novel aspect of the amendment if any :</b>	

**J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE**

**J.1** I hereby ~~confirm that~~/ confirm on behalf of the sponsor that (delete which is not applicable)

- 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.

**J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY (as stated in section D.1):**

J.2.1 Signature <sup>12</sup> 5.1.2.e [REDACTED]

J.2.2 Print name : 5.1.2.e [REDACTED] on behalf of 5.1.2.e [REDACTED]

J.2.3 Date : 23-Jan-2020

**J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section D.2):**

J.3.1 Signature <sup>13</sup>:

J.3.2 Print name:

J.3.3 Date :

<sup>11</sup> Cf. Section 3.7.c. of the detailed guidance CT-1.

<sup>12</sup> On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.

<sup>13</sup> On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.