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 : ☐ Date :
Date of start of procedure:	Authorisation/ positive opinion : ☐ Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application ☐ 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:	**The Netherlands**
A.2 Notification for authorisation to the competent authority:	☒
A.3 Notification for an opinion to the ethics committee:	☒

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] yes ☐ no ☒

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 02, dated 18-December-2018

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

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

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

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.

D APPLICANT IDENTIFICATION (please tick the appropriate box)

D.1	Request for the competent authority	
D.1.1	Sponsor	☐
D.1.2	Legal representative of the sponsor	☐
D.1.3	Person or organisation authorised by the sponsor to make the application	☒
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 :	[redacted]
D.1.4.3	Address :	Metropolis Center, Str. Grigore Alexandrescu, No. 89-97, Bucharest, 010624, Romania
D.1.4.4	Telephone number :	+40 [redacted]
D.1.4.5	Fax number :	+40 [redacted]
D.1.4.6	E-mail:	[redacted]@Novartis.com

D.2	Request for the Ethics Committee	
D.2.1	Sponsor	☐
D.2.2	Legal representative of the sponsor	☐
D.2.1	Person or organisation authorised by the sponsor to make the application.	☐
D.2.2	Investigator in charge of the application if applicable[4]:	
	• Co-ordinating investigator (for multicentre trial)	☐
	• Principal investigator (for single centre trial):	☐
D.2.3	Complete below	
D.2.3.1	Organisation :	
D.2.3.2	Name :	
D.2.3.3	Address :	
D.2.3.4	Telephone number :	
D.2.3.5	Fax number :	
E-mail :		

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1 Sponsor's substantial amendment code number, version, date for the clinical trial concerned:
CCNP520A2202J Protocol Amendment version 02, dated 18-December-2018, Subject leaflet inclusive ICF main study BRC Amsterdam version 3.0 dated 15Jan2019, Subject leaflet inclusive ICF main study BRC Den Bosch version 3.0 dated 15Jan2019, Information leaflet for study partner subject version 2.0 dated 15Jan2019 and Information leaflet summary main study version 2.0 dated 15Jan2019.

E.2	Type of substantial amendment	
E.2.1	**Amendment to information in the CT application form**	yes ☒ no ☐
E.2.2	**Amendment to the protocol**	yes ☒ no ☐
E.2.3	**Amendment to other documents appended to the initial application form**	yes ☐ no ☒
E.2.3.1	If yes specify:	
E.2.4	**Amendment to other documents or information:**	yes ☒ no ☐
E.2.4.1	If yes specify: Informed Consent Form	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented[5]**	yes ☐ no ☒
E.2.6	**This amendment is to notify a temporary halt of the trial[6]**	yes ☐ no ☒
E.2.7	**This amendment is to request the restart of the trial[7]**	yes ☐ 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**	**yes ☒ no ☐**
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	**yes ☐ no ☒**
E.3.3	**Changes in quality of IMP(s)**	**yes ☐ no ☒**
E.3.4	**Changes in conduct or management of the trial**	**yes ☒ no ☐**
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	**yes ☐ no ☒**
E.3.6	**Change/addition of site(s)**	**yes ☐ no ☒**
E.3.7	**Other change**	**yes ☒ no ☐**
E.3.7.1	**If yes, specify:**	

Protocol amendment:

Protocol v02: The main purpose of this amendment is to implement additional monitoring of cognition and neuropsychiatric signs and symptoms for participants and inform participants about the recent findings from other BACE-inhibitors that was implemented following an urgent safety measure (USM).

ICF: The protocol changes affect the informed Consent, and a revised Informed Consent Form (ICF) takes into account the changes described in the protocol amendment.

E.3.8	**Other case**	**yes ☐ no ☒**
E.3.8.1	**If yes, specify**	

E.4	Information on temporary halt of trial[8]	
E.4.1	**Date of temporary halt** (YYYY/MM/DD)	
E.4.2	**Recruitment has been stopped**	yes ☐ no ☐
E.4.3	**Treatment has been stopped**	yes ☐ 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)**:	

- Justification for a temporary halt of the trial
- The proposed management of patients receiving treatment at time of the halt *(free text)*.

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
As described in the CCNP520A2202J Protocol amendment version 02, track changes version, available upon request	As described in the CCNP520A2202J Protocol amendment version 02, clean versio, available upon request	This amendment addresses proactive actions required to enhance the ongoing monitoring of CNP520. The changes to the protocol are required to reflect the Urgent Safety Measure (USM) action plan from 13-November-2018. Other changes include change in dose adaptation strategy by introducing a lower dose regimen (LDR). The decision to introduce the option for DRM and to remove the original potential for adaptation was not driven by data of the clinical trial, but on other sponsor's BACE inhibitor results. In addition, the DRM will keep main design features unchanged including the statistical testing procedure. Changes to specific sections of the

[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.

		protocol are described in track changes version, available upon request

The protocol changes herein affect the Informed Consent, and a revised Informed Consent takes into account the changes described in the protocol amendment. The updated ICF version will be used to re-consent participants already enrolled in the trial and be used for consenting any newly enrolled participant.

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……..)
G.1.1.1.5 Professional address
G.1.2 **Removal of an existing 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……..)
G.1.2.1.5 Professional address
G.1.3 **Change of co-ordinating investigator** (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:
G.1.4 **Change of principal investigator at an existing site** (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

H.1 Change of e-mail contact for feedback on application*

H.2 Change to request to receive an .xml copy of CTA data ☐ yes ☐ no
H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ☐ yes ☐ 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).

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

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	☒
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]	**EC** ☒ CA ☐
I.4 Supporting information	**EC** ☒ CA ☐
I.5 Revised .xml file and copy of initial application form with amended data highlighted	☒
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 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 [12]:

[redacted] 5.1.2.e

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

J.2.3 Date : 07-Feb-2019

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

J.3.1 Signature [13]:

J.3.2 Print name:

J.3.3 Date :

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

[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.