To: ccmo_bi[bi@ccmo.nl]
From: [redacted]
Sent: Mon 15-7-2019 8:36:09
Subject: NL61015.029.17 - CCNP520A2202J -Digital submission of a substantial amendment for approval -USM - Temporary Halt of the trial
Received: Mon 15-7-2019 8:36:32
A1 CCNP520A2202J Cover Letter NL61015.029.17_ 15Jul2019.pdf
B5 CCNP520A2202J Substantial_Amendment_Notification_Early Termination_15Jul2019.pdf

Dear Madam, dear Sir,

On behalf of the Sponsor, Novartis Pharma AG, PAREXEL International Romania s.r.l. herewith submits a substantial amendment to the above referenced clinical trial for review and authorization.

The changes in this amendment relate to:

- **Temporary Halt of the trial CCNP520A2202J as result of an Urgent Safety Measure for all ongoing studies with CNP520**.

We trust that the information provided in the application is sufficient, however if you require any further information, please contact us.

Yours faithfully,

PAREXEL International Romania s.r.l.
[redacted] on behalf of [redacted]
[redacted]
Metropolis Center, 89-97 Grigore Alexandrescu Street
Bucharest, Romania, 010624
Tel: +4031 [redacted]
Fax: +40 372 [redacted]
E-mail: [redacted]@novartis.com

Parexel International Romania s.r.l.
Metropolis Center - Str. Grigore Alexandrescu, Nr.89-97, Sector 1, 010624 Bucharest, Romania
J40/9291/2004; CUI: RO 16494261
Phone: +40 [redacted] / Fax: +40 [redacted] / www.parexel.com

PER E-MAIL TO BI@CCMO.NL
CCMO
Attn. Competent Authority
Parnassusplein 5
2511 VX Den Haag
The Netherlands

Bucharest, 15-Jul-2019

Subject:	**Digital submission of a substantial amendment for approval:** ☐ USM - Temporary Halt of the trial
ToetsingOnline:	NL61015.029.17
EudraCT no.:	2016-002976-28
Protocol code:	CCNP520A2202J
Protocol title:	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)
Sponsor:	Novartis Pharma AG, Lichtstrasse 35, Basel, 4056, Switzerland
EU Legal Rep:	Novartis Pharma Arzneimittel GmbH, Roonstrasse 25, Nürnberg, 90429, Germany

Dear Madam, dear Sir,

On behalf of the Sponsor, Novartis Pharma AG, PAREXEL International Romania s.r.l. herewith submits a substantial amendment to the above referenced clinical trial for review and authorization.

The changes in this amendment relate to:
☐ The addition of a new IMP;
☐ A substantial change of the current IMP
☒ Other, namely:

- ✓ **Temporary Halt of the trial CCNP520A2202J** as result of an Urgent Safety Measure for all ongoing studies with CNP520.

The reasons for this measure are described in the enclosed Annex 2 form.

Novartis, in consultation with its collaboration partners [redacted] and [redacted], has decided to take an urgent safety measure to immediately discontinue assessment of CNP520 in the Alzheimer's Prevention Initiative Generation Program. The Sponsors' decision follows the assessment of unblinded data of the BACE1 inhibitor, CNP520, by the independent Data Monitoring Committee (DMC), during a planned data review on 26 June 2019.

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Key findings from this data review of CNP520 were as follows:

- Consistent mild worsening was observed in some measures of cognitive function. Worse performance on RBANS was observed for CNP520 15 mg and CNP520 50 mg compared to placebo at both Week 13 and 26 in both studies. Increased decline in RBANS of more than 7 points and more than 14 points was detected in the CNP 520 groups versus placebo. A consistent trend in worsening was also observed for CDR-SOB in the CNP520 groups compared to placebo.
- Volumetric MRI (whole brain and hippocampal volume) indicated increased volume loss on active treatment compared to placebo.
- Greater mean weight loss was observed at 26 weeks on CNP520 for both 15 mg and 50 mg doses vs placebo.

The early worsening in some cognitive measures observed with CNP520 appears similar to data reported for other BACE inhibitors. For those BACE inhibitors, the early worsening in some cognitive measures did not show resolution with longer exposure (e.g., Egan et al, 2019, Henley et al, 2019).

Taking into consideration the totality of data available, the Sponsors are not confident that a state of equipoise (in which there is a reasonable balance between known and potential benefits and harms) still exists. Therefore, the decision has been made to discontinue assessment of CNP520 in the Generation program.

The following actions are to be taken as part of this Urgent Safety Measure (USM) in Generation Study 2:

<u>Actions for randomized participants in the Treatment Epoch:</u>

- **Must be informed of this Urgent Safety Measure immediately, but no later than 10 business days from receipt of this notification.**
- Participants must be instructed to **stop the study medication immediately**. (Confirmation of last dose taken must be obtained and documented.)
- All participants still on treatment must return to the site to complete the following visits:
    1. **Modified Treatment Epoch Completion visit** (Visit 299 in Generation Study 2) at any time after receipt of this letter, but no later than their next regularly scheduled 3-monthly visit. The modifications for this visit include the following:
        - MRI, PET and Lumbar Puncture for CSF samples are no longer required at this visit
    2. **Modified End of Study Follow-up visit** (Visit 301 in Generation Study 2). The modifications for this visit include the following:
        - Timing is changed from 3 month post Treatment Epoch Completion visit to 6 month post Treatment Epoch Completion visit:
        - Simplified assessments required at this visit include:

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- AEs and SAEs
- RBANS
- CDR
- Volumetric MRI (3DT1 sequence only)
- Blood biomarker sample

- Participants who had previously discontinued treatment but were still attending study visits prior to this notification, should complete the **modified End of Study Follow-up visit** at any time after the participant has been off study drug for at least 6 months.

Actions for participants in the Screening Epoch:

- Participants must be contacted prior to the next scheduled visit, to inform that Generation Study 2 is being terminated early. These participants are to be classified as screening failures and the reasons recorded as "Study terminated by sponsor" in the eCRF.
- Genetic Disclosure and amyloid disclosure follow-up assessments should continue as per protocol for those who already received their genotype (or amyloid) results.

All Investigators and IRB/IECs are being made of aware of these urgent safety measures. These urgent safety measures as well as a patient management plan post study termination is described in more detail in the Letter to Investigators which is available upon request.

The Declaration of the End of Trial Form, including information regarding early termination of study, will be submitted to each Health Authority once the Last Patient Last Visit (LPLV) occurs in this study.

Please find the following study documents supporting this request for approval attached to this e-mail:

CCMO numbering	Document	Version /Date
A.	**Letter**	
A1	Cover Letter	15-Jul-2019
B.	**Forms**	
B5	Substantial_Amendment_Notification_Form_CNP520	15-Jul-2019

According to the regulatory requirements of the Netherlands, it is required to submit only the applicable EudraCT forms to support a substantial amendment submission.

Therefore, the following documents are not attached, but are available upon request:

Parexel International Romania s.r.l.
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CCMO numbering	Document	Version /Date
K.	**Other Relevant Documents**	
K6	Investigator letter for Generation Program CNP520 discontinuation	11-Jul-2019

With this submission, we declare that all relevant documents of the present submission dossier are signed by the persons authorised for this task.

We trust that the information provided in the application is sufficient, however if you require any further information, please contact us.

Yours faithfully,

PAREXEL International Romania s.r.l.
5.1.2.e on behalf of 5.1.2.e
5.1.2.e
Metropolis Center, 89-97 Grigore Alexandrescu Street
Bucharest, Romania, 010624
Tel: +4031 5.1.2.e
Fax: +40 372 5.1.2.e
E-mail: 5.1.2.e @novartis.com

5.1.2.e

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

D APPLICANT IDENTIFICATION (please tick the appropriate box)

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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.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: 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 31 5.1.2.e	
D.1.4.5	Fax number: +40 372 5.1.2.e	
D.1.4.6	E-mail: 5.1.2.e @Novartis.com	

D.2	Request for the Ethics Committee	
D.2.1	Sponsor	☐
D.2.2	Legal representative of the sponsor	☐
D.2.3	Person or organisation authorised by the sponsor to make the application.	☐
D.2.4	Investigator in charge of the application if applicable[4]:	
☐	Co-ordinating investigator (for multicentre trial)	☐
☐	Principal investigator (for single centre trial):	☐
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

E.1 Sponsor's substantial amendment code number, version, date for the clinical trial concerned:
Temporary Halt – Early Termination of the Generation Study 2 of the study CCNP520A2202J

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:	
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:**	
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** (2019/07/11)

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:

Overall, 1,136 patients are still in the treatment period at time of early termination in study CCNP520A2202J.

CCNP520A2202J	
Country	**Number of Patients**
Belgium	3
Finland	14
France	1
Germany	0
Iceland	129
Netherlands	22
Portugal	8
Spain	37
Switzerland	11
UK	155
Argentina	0
Chile	5
South Korea	16
Mexico	6
Singapore	3
South Africa	1
Taiwan	3
Australia	10
Canada	36
China	0
Israel	6
Italy	0
Japan	28
USA	642

E.4.5 **Briefly describe (free text)**:

☐ **Justification for a temporary halt of the trial**

The Sponsor's decision to terminate early study CCNP520A2202J was made on July 8, 2019 and follows the assessment of unblinded data of the BACE1 inhibitor, CNP520, by the independent Data Monitoring Committee (DMC), during a planned data review on June 26, 2019.

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

Key findings from this data review of CNP520 were as follows:

- Consistent mild worsening was observed in some measures of cognitive function. Worse performance on RBANS was observed for CNP520 15 mg and CNP520 50 mg compared to placebo at both Week 13 and 26 in both studies. Increased decline in RBANS of more than 7 points and more than 14 points was detected in the CNP 520 groups versus placebo. A consistent trend in worsening was also observed for CDR-SOB in the CNP520 groups compared to placebo.
- Volumetric MRI (whole brain and hippocampal volume) indicated increased volume loss on active treatment compared to placebo.
- Greater mean weight loss was observed at 26 weeks on CNP520 for both 15 mg and 50 mg doses vs placebo.

The early worsening in some cognitive measures observed with CNP520 appears similar to data reported for other BACE inhibitors.

Taking into consideration the totality of data available, the Sponsors are not confident that a state of equipoise (in which there is a reasonable balance between known and potential benefits and harms) still exists. Therefore, the decision has been made to discontinue assessment of CNP520 in the Generation program.

A temporary halt in study is reflected herein for study CCNP520A2202J detailing the reasons for the early termination of study. The Declaration of the End of Trial Form, including information regarding early termination of study, will be submitted to each Health Authority once the Last Patient Last Visit (LPLV) occurs in this study.

☐ **The proposed management of patients receiving treatment at time of the halt** *(free text)*.

Please refer to the actions to be taken as part of this Urgent Safety measure in Investigator Notification – Urgent Safety Measure (USM) letter provided along with this notification.

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)*.

At the time of early termination of Study CCNP520A2202J is not available for evaluation. Study results will be further evaluated at the completion of the follow-up phase of the study and a study report will be provided to Health Authorities.

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
Not Applicable	Not Applicable	

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

G.1 Type of change

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

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).	

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]	☐
I.4 Supporting information	**EC** ☐ **HA** ☐

[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.

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): ☐

5.1.2.e

J.2.1 Signature [12]:

J.2.2 Print name : 5.1.2.e on behalf of 5.1.2.e

J.2.3 Date : 15-Jul-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 :

[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.