

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

23-Jan-2020

Subject:	Digital Submission of Substantial Amendments to a Clinical Trial: <ul style="list-style-type: none">• Protocol Amendment version 03, dated 07-Jan-2020• CNP520 Investigator's Brochure Edition 6, dated 23-Aug-2019
ToetsingOnline	NL61015.029.17
Dossier no:	
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/Sir,

On behalf of the Sponsor, **Novartis Pharma AG**, Parexel International Romania s.r.l. as the applicant herewith submits substantial amendments to the above referenced clinical trial for review and authorization.

The changes in these amendments relate to:

- **Protocol Amendment version 03, dated 07-Jan-2020**
- **CNP520 Investigator's Brochure Edition 6, dated 23-Aug-2019, replacing Edition 5 dated 21-Aug-2018**

The reasons of changes are described in Sections F of the enclosed Annex 2 form.

- **CCNP520A2202J Protocol Amendment version 03, dated 07-Jan-2020**

Following our Urgent Safety Measure (USM) communication submitted to CCMO on 15-July-2019, detailing the decision to terminate early CCNP520A2202J, as well as the communication notified to CCMO on 05-August-2019 and 13-December-2019, providing clarifications to the Participant Follow-up Plan, we are now submitting the Protocol Amendment Version 03, available upon request, that administratively describes the early study termination and the modifications to the Participant Follow-Up Plan implemented as part of the USM.

The summary/ list of changes made to the previous version are described at pages 13-14 of the Protocol, available upon request.

Changes to specific sections of the protocol are described in the track changes version of the protocol using strikethrough red font for deletions and red underlined for insertions, available upon request.

Ensuing from this amendment the Informed Consent Form was updated, however, in the Netherlands no revised ICF addendum will be created to inform the patients about the changes of protocol amendment version 03. The reason is that all patients are already verbally informed as per the Follow-up #2 USM notification dated 12-Dec-2019, which included Information for Study Participants. This information was to be shared verbally with ongoing participants that came for their scheduled mEoS visit on site or during the phone contact prior to local EC/IRB approval of the revised ICF addendum with the appropriate note made in the source documentation. As all patients have been verbally informed already, (this has been documented in the source) and as all study participants will have had their EoS visit by the time protocol amendment version 03 will be approved, no revised ICF will be referred to with protocol amendment version 03.

The final study reports will be available for submission to HAs within 12 month after the LPLV from the Participant Follow-up phase. Novartis remains committed to advancing science in Alzheimer's disease and to presenting and sharing the program data when available within a final study report.

EudraCT Application Form

The sections A.4.2, A.4.3 of the EudraCT application form were updated to be in line with this amendment with revised sections highlighted in the enclosed updated pdf-version.

- **CNP520 Investigator's Brochure Edition 6, dated 23-Aug-2019, replacing Edition 5 dated 21-Aug-2018**

The current Investigator's Brochure (IB) update to edition 6 is an annual update. The information on IB is updated with recent non-clinical and clinical trial information in the field of Alzheimer's prevention and treatment and information added about urgent safety measure (USM) for stopping assessment of CNP520 in the ongoing clinical studies.

Key changes made to the IB and rationale for these changes are described in the "Summary of key changes from Edition 6 to Edition 5" included in the Investigator's Brochure at page 3 and, in addition, a separate Summary of Changes is available upon request.

Overall Risk-Benefit:

With the changes introduced in this edition of the IB, the risk/benefit assessment of (CNP520) is **altered/changed** for people at risk for the onset of clinical symptoms of Alzheimer's disease (according to protocols **buiten reikwijdte verzoek** and CNP520A2202J)

On 11-Jul-2019, an Investigator Notification - Urgent Safety Measure (USM) was issued to discontinue assessment of CNP520 in the two Phase II/III studies in the Generation Program (**buiten reikwijdte verzoek** Cohort II, and CCNP520A2202J). The decision followed the assessment of unblinded data, by the independent Data Monitoring Committee (DMC), during a planned data review on 26 June 2019. Main observation was consistent mild worsening in some measures of cognitive function in subjects receiving CNP520 as compared to subjects receiving placebo.

Reference Safety Information

No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the DSUR for the IMP.

More details of the changes may be found in track changes version of this IB and in the Summary of changes documents, both enclosed available upon request.

The Investigator's Brochure update has no impact on the ICF and protocol.

Please find attached to this e-mail the following study documents supporting this notification:

CCMO numbering	Document	Version /Date
A.	Letter	
A1	Cover Letter	23-Jan-2020
B.	Forms	
B3a B3b B3c	Revised EudraCT Application Form <ul style="list-style-type: none"> ✓ PDF copy highlighted ✓ XML file ✓ Validation Report 	22-Jan-2019 <i>XML File Identifier:</i> <i>K+8kkKj5g+D44L+j1UYuPIHwagU=</i>
B5	Substantial Amendment Notification Form	23-Jan-2020

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:

CCMO numbering	Document	Version /Date
C.	Protocol related	
C1a	Protocol CCNP520A2202J <i>Clean</i>	V03/07-Jan-2020
C1b	Protocol CCNP520A2202J <i>Track changes</i>	V03/07-Jan-2020
D.	Product Information	
D1a	CNP520 Investigator's Brochure (<i>Clean and Tracked changes versions</i>)	V6/23-Aug-2019
D1b	CNP520 Investigator's Brochure Summary of changes	V6/23-Aug-2019

With this submission, we declare that all relevant documents of the present submission dossier are signed by the persons authorized 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

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on behalf of 5.1.2.e

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