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: +4031 5.1.2.e / Fax: +4031 5.1.2.e / www.PAREXEL.com

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

07-Feb-2019

Subject: **Digital Submission of a Substantial Amendment for approval:**
- **Protocol Amendment version 02 dated 18-December -2018**

ToetsingOnline Dossier no:	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/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: **Protocol:** Clinical Trial Protocol Amendment 02 dated 18 December 2018

The reasons for these changes are described in Section F of the enclosed Annex 2 form.

Protocol: Clinical Trial Protocol Amendment 02 dated 18 December 2018:
This amendment primarily 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 13Nov2018. Other changes to the protocol include change in dose adaptation strategy by introducing a lower dose regimen option, incorporation of changes required by local health authorities and clarifications of different administrative aspects of the protocol.

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: +4031 5.1.2.e / Fax: +4031 5.1.2.e / www.PAREXEL.com

The USM was triggered by the data disclosed about two other BACE inhibitors indicating an increase in neuropsychiatric events along with a decline in cognition starting in the first 3 to 6 months of treatment. The protocol is therefore amended to include an additional cognitive assessment with RBANS at the 3 month visit, as well as the NPI-Q at 3 and 6 months and every 6 months thereafter.

Results from studies of two other compounds with the same mechanism of action did not indicate a decline in cognitive performance or increase in neuropsychiatric events, making it difficult to know whether the negative effects reported for some of the other compounds are due to BACE inhibition per se or due to other properties of the drugs. The available data from other sponsors indicate that the early effects on cognition were found with doses of BACE inhibitors leading to at least 60 % reduction of Aβ in CSF. The doses of CNP520 in this study, 50 mg and 15 mg, achieve 86% and 68% median reduction of CSF Aβ, respectively.

In light of the new data from some other BACE inhibitor compounds, potential lower dose regimen options targeting less than 60% reduction of CSF Aβ are being incorporated into the protocol. Such dose regimen modification (DRM process) could be activated upon DMC recommendation after review of CNP520 data and/or in light of new data on either CNP520 or other BACE inhibitors. While the protocol previously included an adaptive design allowing a dose reduction from the current 50 mg to 15 mg once daily dose, this amendment removes the original adaptation process since these two doses are deemed to be too close in terms of CSF Aβ lowering and replaces it with the DRM.

Summary/ list of changes made to the previous version are described in the pages 13-15 of the Protocol and are 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.

Ensuing from this amendment the Informed Consent Form was updated.

Additional information:
This is to inform you that the potential future 6 mg dosage strength described in the protocol is not yet included to the IMPD and will be added shortly and provided to Health Authorities for approval.
The 6 mg Lower dose Regimen will not be implemented until approval

EudraCT Application Form
The sections A.4.2, A.4.3, E.3 and E.4 of the EudraCT application form were updated to be in line with this amendment with revised sections highlighted in the enclosed updated pdf-version.

PAREXEL
YOUR JOURNEY. OUR MISSION.™

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: +4031 5.1.2.e / Fax: +4031 5.1.2.e / www.PAREXEL.com

Additional EudraCT application Form updates:

- The Sponsor contact person was changed, section B.1
- A typo was observed and corrected in section E.6.9
- Since the previous submission, updates have been made to the list of Participating Countries, section E.8.6.3; Sections D.2.4.1 were also updated
- Section E.8.10.2 was updated to reflect the current situation
- Section F.4.1 has been updated from 40 to 30 patients
- Vendor addition/ removal, Vendor information updates, section G.3 and G.5.

The EudraCT form was updated accordingly.

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	07-Feb-2019
B	**Forms**	
B3a B3b B3c	Revised EudraCT Application Form ✓ PDF copy highlighted ✓ XML file ✓ Validation Report *XML File Identifier: Z/948hnPu/x1oBZr6E7cs//0yj0=*	05-Feb-2019
B5	Substantial Amendment Notification Form	07-Feb-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:

CCMO numbering	Document	Version /Date
C	**Protocol related**	
C1a	Protocol CCNP520A2202J v2.0 Clean	V2.0/18-Dec-2018
C1b	Protocol CCNP520A2202J v2.0 Track changes	V2.0/18-Dec-2018

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: +4031 5.1.2.e / Fax: +4031 5.1.2.e / www.PAREXEL.com

C1c	Protocol CCNP520A2202J Version 2.0 Sponsor Signature Page	20-Dec-2018
E.	**Information for the research subject**	
E1.E2a	Subject leaflet inclusive ICF main study BRC Amsterdam - Clean and Tracked changes	V3.0/15-Jan-2019
E.E2b	Subject leaflet inclusive ICF main study BRC Den Bosch - Clean and Tracked changes	V3.0/15-Jan-2019
E4a	Information leaflet for study partner subject - Clean and Tracked changes	V2.0/15-Jan-2019
E4b	Information leaflet summary main study - Clean and Tracked changes	V2.0/15-Jan-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 SRL
5.1.2.e on behalf of 5.1.2.e
Metropolis Center, Str. Grigore Alexandrescu, No. 89-97
Bucharest, Sector 1, Romania, 010624

5.1.2.e

Tel : +4.031 5.1.2.e
Fax: +40 0372 5.1.2.e
Email: 5.1.2.e @Novartis.com