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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 5.1.1.c and 5.1.1.c, 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:

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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.
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