

To: ccmo_frontoffice[frontoffice@ccmo.nl]
From: ccmo_bi
Sent: Mon 5-8-2019 9:08:17
Subject: FW: NL61015.029.17 - CCNP520A2202J -Digital submission of Investigator Notification following the 11 July 2019 Urgent Safety Measure
Received: Mon 5-8-2019 9:08:19
[A1 CCNP520A2202J Cover Letter NL61015.029.17_05Aug2019.pdf](#)
[K6 CCNP520A2202J Investigator letter 2 for Generation Program CNP520 discontinuation 1Aug2019.pdf](#)

Voor MArjolein

Van: [REDACTED] 5.1.2.e @novartis.com > Namens [REDACTED] 5.1.2.e
Verzonden: maandag 5 augustus 2019 09:58
Aan: ccmo_bi <bi@ccmo.nl>
Onderwerp: NL61015.029.17 - CCNP520A2202J -Digital submission of Investigator Notification following the 11 July 2019 Urgent Safety Measure

Dear Madam, dear Sir,

On behalf of the Sponsor, Novartis Pharma AG, PAREXEL International Romania s.r.l. herewith submits the Investigator Notification letter dated 01 August 2019.

Following our Urgent Safety Measure(s) detailing the decision to terminate study CCNP520A2202J and the termination of Cohort II in Study CAPI015A2201J as well as the participants follow-up plan, it has been decided to issue a follow-up Investigator Notification to provide more detailed guidance on participants management in these studies beyond what was specified in the original USM Investigator Notification letter submitted to the Netherlands Health Authority on date 15 July 2019.

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] 5.1.2.e on behalf of [REDACTED] 5.1.2.e

Metropolis Center, 89-97 Grigore Alexandrescu Street
Bucharest, Romania, 010624
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PER E-MAIL TO BI@CCMO.NL

CCMO

Attn. Competent Authority

Parnassusplein 5

2511 VX Den Haag

The Netherlands

Bucharest, 05-Aug-2019

Subject: Digital submission of Investigator Notification following the 11 July 2019 Urgent Safety Measure

**Investigator Notification for Generation Program:
CCNP520A2202J (Generation Study 2)**

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 the Investigator Notification letter dated 01 August 2019.

Following our Urgent Safety Measure(s) detailing the decision to terminate study CCNP520A2202J and the termination of Cohort II in Study [redacted] **buiten reikwijdte verzoek** as well as the participants follow-up plan, it has been decided to issue a follow-up Investigator Notification to provide more detailed guidance on participants management in these studies beyond what was specified in the original USM Investigator Notification letter submitted to the Netherlands Health Authority on date 15 July 2019.

Reference is made to study CCNP520A2202J (EudraCT No. 2016-002976-28) randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy of two doses of CNP520 (15 mg and 50 mg) in participants at risk for the onset of clinical symptoms of AD.

This letter is to inform you that Novartis, with its collaboration partners [redacted] 5.1.1.c and [redacted] 5.1.1.c [redacted], after consultation with the Investigators and Alzheimer scientific community made modifications to the initially proposed follow-up patient management plan. The detailed updated follow-up patient

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management action plan is described in the Investigator Notification attached to this letter.

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

Numbering	Document	Version /Date
A.	Letter	
A1	Cover Letter	05-Aug-2019
K.	Other Relevant Documents	
K6	Investigator letter 2 for Generation Program CNP520 discontinuation	01-Aug-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.

[redacted] on behalf of [redacted]

Metropolis Center, 89-97 Grigore Alexandrescu Street
Bucharest, Romania, 010624

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[redacted]
5.1.2.e



Investigator Notification

Date: 01 August 2019
To: All investigators involved in the Generation Program

**Re: Investigator Notification following the 11 July 2019 Urgent Safety Measure
Investigator Notification for Generation Program: [buiten reikwijdte verzoek]
[redacted] and CCNP520A2202J (Generation Study 2)**

Dear Investigator,

This letter is in follow-up to the initial Investigator Notification (dated 11 July 2019) re: discontinuation of CNP520 treatment.

- 1. Modified Treatment Epoch Completion Visit** (Visit 399 in [buiten reikwijdte verzoek] and Visit 299 in Generation Study 2): Noted in the initial Investigator Notification (dated 11 July 2019): MRI, PET and Lumbar Puncture for CSF samples are no longer required at this visit.
 - Although not required, we **recommend that the full MRI scan is completed if the participant's upcoming scheduled visit includes an MRI** (Month 6, Month 12, Year 2) **or if they have not had a full MRI in the last 6 months**, as this is a prudent safety assessment to complete at Treatment Epoch Completion.
 - Additionally, if participants who already had a baseline CSF sample collected are willing, an additional **CSF sample should be collected at this visit** and will be analyzed for biomarkers. This will help us to evaluate if there are markers associated with cognitive decline and/or imaging findings.
 - PET assessments, both tau and amyloid, are not to be completed. Ligands will not be provided.
- 2.** This letter also specifies an **Interim Telephone Check-in Point**, to occur approximately 3 months after Treatment Epoch Completion Visit. This visit is limited to a telephone call as a touch point for confirming scheduling for the Modified End of Study Follow-up Visit.

Appendix 1 and **Appendix 2** of this letter are revised assessment schedules for Generation Study 1 and Generation Study 2, respectively, summarizing the full assessments schedule to be performed at the Modified Treatment Epoch and Modified End of Study Follow-up Visits.

These Urgent Safety Measure follow-up actions are to be implemented immediately, prior to IRB/IEC or Health Authority approval. Please provide this notification to your IRB/IEC review board without delay.

The Sponsor will notify the National Health Authority of these Urgent Safety Measure follow-up actions in parallel with this notification.

We thank you again for your continued support in taking these important actions. We look forward to the times when we can share the results and data with you, for both the purpose of educating your participants and to inform the Alzheimer's community at large.

Sincerely,

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Novartis Pharmaceuticals

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Novartis Pharma AG

Appendix 2: Generation Study 2: Revised Visit schedule under USM

Modified Visit Evaluation Schedule under USM in Generation Study 2		
Epoch	Treatment	Follow-up
Visit Name	Modified PPW/TEC ^d	Modified EOS ^e
Visit Number	Visit 299	Visit 301
MCI / Dementia Diagnostic Classification	X	X
Physical/Skin/Neurological Exam	X	Not required ^f
Electrocardiogram (ECG)	X	Not required ^f
Vital Signs (including weight)	X	X
Laboratory evaluations	X	Not required ^f
MRI	X ^a	X ^g
Lumbar puncture and CSF Biomarkers ^b	X	NA
Blood Biomarker (serum/plasma and RNA pharmacogenomics) ^c	X	X ^h
MMSE	X	X
RBANS (APCC)	X	X
Raven's (APCC)	X	X
GDS	X	Not required ^f
CDR	X	X
ECog	X	X
NPI-Q	X	X
QoL-AD	X	Not required ^f
Lifestyle Questionnaire	X	Not required ^f
AE/SAE	X	X
eC-SSRS	X	X
Concomitant medications	X	X
Pharmacokinetic sample (for CNP520 and additional blood biomarkers)	X	Not required ^f

^a Although not required, it is recommended that the **full MRI scan is completed if the participant's upcoming scheduled visit includes an MRI** (Month 6, Month 12, Year 2) **or if they have not had a full MRI in the last 6 months.**

^b For participants who already had a baseline CSF sample collected and are willing, additional CSF samples should be collected as per protocol at this visit. Ensure participant consented to the additional optional procedures. No CSF cell counts required.

^c Ensure participant consented to the additional optional procedures.

^d An Interim Telephone Check-in Point Visit will occur approximately 3 months after Treatment Epoch Completion. This visit is limited to a telephone call as a touch point for confirming scheduling for the Modified End of Study Follow-up visit

^e NEW: The modified EOS visit will be done at **6 months** (\pm 4 weeks) from the modified TEC/PPW visit.

^f NEW: Assessment no longer required during the modified EOS visit.

^g NEW: Only **volumetric MRI (3DT1 sequence only)** is required during the modified EOS visit.

^h NEW assessment to be completed during the modified EOS visit.

NA: Not applicable