To: ccmo_bi[bi@ccmo.nl]
Cc: [redacted]@novartis.com]
From: [redacted]
Sent: Fri 13-12-2019 17:17:12
Subject: NL61015.029.17 - CCNP520A2202J -Digital submission of Investigator letter 3 (Follow-up#2) for Generation Program CNP520 discontinuation_12Dec2019
Received: Fri 13-12-2019 17:17:49
A1 CCNP520A2202J Cover Letter NL61015.029.17_ 13Dec2019..pdf
K6 CCNP520A2202JInvestigator letter 3 (Follow-up#2) for Generation Program CNP520 discontinuation_12Dec2019.pdf

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 12 December 2019.
Following our Urgent Safety Measure (USM) communication sent to your attention on 15 July 2019 detailing the decision to terminate study CCNP520A2202J (which included a Participants Follow-Up plan as part of the Investigator's Notification) as well as our communication to you on 05 August 2019 providing clarifications to the Participant Follow-up Plan, Novartis in collaboration with its partners at [redacted] and [redacted], has decided to issue a 2nd Investigator Notification to further streamline assessments in the Participant Follow-up Plan post discontinuation of CNP520 treatment.
We trust that the information provided in the application is sufficient, however if you require any further information, please contact us.
Yours faithfully,

[redacted] **on behalf of applicant** [redacted]
Novartis HUB
Telephone: +40 [redacted]
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CCMO
Attn. Competent Authority
Parnassusplein 5
2511 VX Den Haag
The Netherlands

Bucharest, 13-Dec-2019

Subject: **Digital submission of Investigator Notification following the 11 July 2019 Urgent Safety Measure and Follow-Up Investigator Notification dated 01 August 2019**

- **Investigator letter notification 3 (Follow-up#2) for Generation Program CNP520 discontinuation 12 December 2019**

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 letter 3 (Follow-up#2) for Generation Program CNP520 discontinuation dated 12 December 2019.

Following our Urgent Safety Measure (USM) communication sent to you on 15 July 2019 detailing the decision to terminate study CCNP520A2202J (which included a Participants Follow-Up plan as part of the Investigator's Notification) as well as our communication to you on 05 August 2019 providing clarifications to the Participant Follow-up Plan, Novartis in collaboration with its partners at 5.1.1.c and 5.1.1.c has decided to issue a 2nd Investigator Notification to further streamline assessments in the Participant Follow-up Plan post discontinuation of CNP520 treatment.

At this time, Novartis is notifying the respective competent authorities regarding changes to the USM Participant Follow-Up Plan (see Investigator Notification attached for details) at the same time that it is communicated to all participating Investigators and Ethics Committees.

Based on changes to the Participant Follow-up Plan from the three Investigator Notifications (submitted to health authorities and ethic committees) in July, August, and now December, Novartis will be amending both study protocols in January 2020 to administratively reflect the early study terminations and the complete modifications to

the Participant Follow-Up Plan implemented as part of the USM. In January 2020, Novartis will submit the amended protocols as an administrative update for completeness of documentation.

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.

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

Numbering	Document	Version /Date
A.	**Letter**	
A1	Cover Letter	13-Dec-2019
K.	**Other Relevant Documents**	
K6	Investigator letter 3 (Follow-up#2) for Generation Program CNP520 discontinuation	12-Dec-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,

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PAREXEL International Romania s.r.l.
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Investigator Notification

Date: 12 December 2019

To: All investigators involved in the Generation Program (buiten reikwijdte verzoek and CCNP520A2202J)

Re: Follow-up #2 to USM: **Streamlining assessments at the modified End of Study visit**

Previous related communications:
11 July 2019: Urgent Safety Measure (USM) / Early termination of CNP520
01 Aug 2019: Follow-up #1 to USM - Investigator Notification

Dear Investigator,

This letter is in follow-up to the previous Investigator Notifications (Urgent Safety Measure (USM) dated 11 July 2019 and Follow-up #1 dated 1 August 2019) regarding early discontinuation of CNP520 treatment in the Generation Program (buiten reikwijdte verzoek and Generation Study 2: CCNP520A2202J). Treatment was discontinued in July 2019 due to the unexpected, mild, early worsening that was observed in some measures of cognition in the active treatment arm.

The purpose of this notification is to inform you that following a recent unblinded analysis that demonstrated **reversal of the worsening in key measures of cognition upon CNP520 treatment discontinuation** (Appendix 1), Novartis, in consultation with its collaboration partners 5.1.1.c and 5.1.1.c , has decided **to streamline the assessments required at the modified End of Study visits** (mEoS). Taking into account the new data, scheduling constraints and burden to participants, the Sponsors concluded that cognitive and volumetric MRI assessments at the mEoS visits are no longer required across both studies buiten reikwijdte verzoek and all participants in Generation Study 2) and does not need to be performed from the receipt of this notification. Assessments for adverse events, concomitant medications, eCSSRS and measurement of body weight during the mEoS remain unchanged (Appendix 2).

The new unblinded analysis of the data from the visits conducted within 1 to 8 weeks after wash-out of the study medication indicates that key cognitive findings are reversible:

- The between-group differences in total RBANS, RBANS Immediate Memory Index and RBANS Delayed Memory Index observed on-treatment were no longer seen after wash-out (i.e. effect sizes ≤0.1, Appendix 1).

- There was no imbalance in the proportion of participants having a ≥14-point decrease in total RBANS or ≥ 1-point increase in CDR-SB after wash-out, while such imbalances were observed at the visits before washout.

Additional data indicate that weight loss and brain volume findings appeared to persist at these same visits conducted shortly after washout:

- Clinically notable weight loss (defined as ≥7% change from baseline) was more frequent on CNP520 than placebo after washout (16% and 6%, respectively), similarly as at week 26 (11% and 3%).

- In a limited dataset with MRI scans (n=89), similar small increase in brain volume loss was observed after washout in actively treated participants compared to placebo. However, there was no correlation of brain volume change with change in total RBANS in the CNP520 treatment group for any of the visits (before or after washout, all R^2<0.2 for whole brain and hippocampus). In addition, these new preliminary analyses show no treatment-related difference in brain volumes at week 26 for the subgroup of participants without elevated brain amyloid (i.e., in about –one-third of the APOE4 homozygotes randomized), although effects on cognition were seen in this important subgroup that were similar to the effects on cognition as seen in the overall population.

  The underlying cause of these volume changes is unknown. With verubecestat, which showed comparable findings, detailed analyses suggested that volume changes are not associated with a generalized, widespread or progressive neurotoxic effect but may be related to specific effects on amyloid related processes (Sur et al, 2019). Further, similar effects were also observed as a consequence of treatment with amyloid immunotherapies (Novak et al, 2016).

  With CNP520, there is no evidence from studies in animals or earlier studies in humans that indicate accelerated neuronal loss following CNP520 treatment. Our new data on reversal of cognitive effects in the overall population and lack of brain volume changes in participants without elevated amyloid also support the hypothesis that volume changes are not indicative of safety concerns, but are related to effects on the existing amyloid pathology.

The final analyses of the Generation Program data will help clarify the initial effects of BACE inhibitors in cognitively unimpaired individuals with or without elevated brain amyloid at genetic risk for AD. These will be detailed in the final clinical study reports.

Please provide this notification to your IRB/Ethics Committees. The Sponsor will notify the Health Authorities at the same time.

We ask you to inform verbally the ongoing participants and document the communication using Appendix 4. Please also read Appendix 2 for scheduling considerations and Appendix 3 for Information to Participants.

Novartis will be amending both study protocols as administrative updates for completeness of documentation to reflect the USM and subsequent changes to the mEoS visits described in the Follow-up #1 and this Follow-up #2 (Investigator Notifications submitted to Health Authorities and IRBs/Ethics committees in July, August, and now December 2019). These amendments including corresponding revised Information for Participant and Consent Form will be provided to you in January 2020.

We thank you for your commitment to the timely conduct of the Treatment Epoch Completion visits and for your continued support in making note of these important study updates.

We look forward sharing the results and data with you and the Alzheimer's community at large.

Sincerely

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Novartis Pharma AG

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Novartis Pharma AG

Appendices:
Appendix 1: November 2019 Cognitive analysis summary
Appendix 2: Operational considerations
Appendix 3: Information to Study Participants
Appendix 4: Study Participant contact form

References:
Novak G, Fox N, Clegg S, et al. Changes in Brain Volume with Bapineuzumab in Mild to Moderate Alzheimer's Disease. Journal of Alzheimer's Disease 49 (2016) 1123–1134.

Sur C, Kost J, Scott D, et al. Verubecestat-Induced Brain Volume Loss Occurs Rapidly and Only in Amyloid-Enriched Brain Regions in EPOCH, a Phase 3 Trial in Mild-to-Moderate Alzheimer's Disease Patients. Alzheimer's & Dementia: The Journal of the Alzheimer's Association (2019) 15(7), P909.

Appendix 1: November 2019 Cognitive analysis summary

The post-treatment discontinuation data were separated for TEC assessments performed before / after washout (i.e. up to / beyond 31 days after the last dose, respectively).

	Week 26 Visit	Treatment Epoch Completion (TEC) Visit	
N participants on CNP520 / placebo[1]	**All**	**TEC before wash-out**[2]	**TEC after wash-out**[2]
	649	610	490
	Cohen's d ES[3] (80% CI) CNP520 vs placebo		
RBANS Total score	-0.27 (-0.38,-0.17)	-0.23 (-0.34,-0.12)	-0.10 (-0.22,+0.02)
Immediate Memory Index	-0.37 (-0.47,-0.27)	-0.22 (-0.32,-0.11)	-0.09 (-0.21,+0.03)
Delayed Memory Index	-0.23 (-0.33,-0.13)	-0.29 (-0.40,-0.19)	-0.10 (-0.22,+0.02)

Change from baseline	Week 26 Visit		Treatment Epoch Completion (TEC) Visit		
	Placebo	**CNP520**	**Placebo**[4]	**CNP520 before wash-out**[2]	**CNP520 after wash-out**[2]
N with both RBANS and CDR at the visit	260	374	441	339	281
			Proportion of participants with		
Decline in RBANS of ≥14 points (1 SD from normal)	10%	16%	9%	14%	7%
Increase in CDR-SB ≥1 point	5%	7%	9%	9%	5%

Notes:

[1] Participants with at least 2 months of treatment and non-missing data for any RBANS index score

[2] 25 Aug 2019 selected as cut-off date for before / after wash-out classification based on 25 July estimated last day of dosing (i.e. USM released 11 Jul 2019 + 2 weeks notification period) and additional 31 days washout.

[3] The effect size will follow the Cohen's d formula using the raw (not model based) mean to standard deviation ratio. The effect size was calculated as the difference between active and placebo in mean change from baseline divided by the pooled standard deviation of the change. Cohen's d= 0.2 is considered a 'small' effect size; 0.5 represents a 'medium' effect size and 0.8 a 'large one'; negative number = in favor of placebo

[4] Single Placebo group analysis at TEC (no split by before / after wash-out for controls)

Results presented in this table are based on interim analysis using 7 Nov 2019 dataset.
Final data will be only available after Database Lock.

Appendix 2: Operational considerations

For [redacted] and Generation Study 2:

The modified End of Study (mEoS) visits are streamlined as follows:

- Modified EoS visits can be scheduled anytime after receipt of this notification but **no later than 15-Mar-2020**. (i.e. the requirement from 11 July 2019 USM for the 6 month timeframe between modified TEC and mEoS visits is no longer required.)
- Only required assessments at mEoS: Adverse Events, Concomitant Medications, eCSSRS and Body weight. An overview of all assessments to be performed is shown in the table below. The assessments outlined in the column titled Follow-up #2 to USM 12 Dec 2019 are to be performed at the upcoming mEoS visits:

Modified EoS Assessment	Follow-up #1 to USM 01 Aug 2019	**Follow-up #2 to USM 12 Dec 2019**
MCI / Dementia Diagnostic Classification	X	**No longer required**
Physical/Skin/Neurological Exam	Not required	**-**
Electrocardiogram (ECG)	Not required	**-**
Vital Signs (including weight)	X	**X: Body weight only (if in-person visit)**
Laboratory evaluations	Not required	**-**
MRI	Added	**No longer required**
Lumbar puncture and CSF Biomarkers	NA	**-**
Blood Biomarker (serum/plasma and RNA pharmacogenomics)	Added	**No longer required**
MMSE	X	**No longer required**
RBANS (APCC)	X	**No longer required**
Raven's (APCC)	X	**No longer required**
GDS	Not required	**-**
CDR	X	**No longer required**
ECog	X	**No longer required**
NPI-Q	X	**No longer required**
QoL-AD	Not required	**-**
Lifestyle Questionnaire	Not required	**-**
AE/SAE	X	**X**
eC-SSRS	X	**X (if in-person visit)**
Concomitant medications	X	**X**
Pharmacokinetic sample (for CNP520 and additional blood biomarkers)	Not required	**-**

Additional operational considerations are noted below:

- Interim Telephone Check-in Point, if still pending, can be used to inform participants verbally of the streamlining of the assessments. Alternatively, at site discretion, this phone call can be skipped and/or replaced by the mEoS.
- Although the mEoS visits are generally expected to be in-person at the site, a phone contact may be considered as mEOS in case of logistical constrains, travel limitations, or personal preference from the participant.
- If the mEoS is conducted as a phone contact, adverse events and/or concomitant medication changes can be reported over the phone, but eCSSRS and body weight will not be recorded.
- Study partners will no longer be required to attend the mEOS visit, and there are no respective ICF requirements for the study partners.
- Please refer to Appendix 3 for information to participants. Please share this information verbally with participants that will come for their mEoS on site prior to local EC/IRB approval of a revised ICF addendum. Streamlined assessments should be implemented at the scheduled mEoS after participants are informed and consent to the changes (verbally or in writing as applicable), with the appropriate note made in study documentation referring to Appendix 4.
- Treatment codes for individual participants in will be released after Database lock

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The sponsors are committed to sharing results of the Generation Program with participants and the AD research community. Please reach out to your local country medical contact or your CRA should you have any questions.

More detailed timelines regarding data cleaning and resolution of queries will be communicated by your local CRA.

Appendix 3: Information to Study Participants

We ask you to contact all participants in [redacted] and Study CCNP520A2202J and inform them verbally about the measures described above. The date of and the means (phone or in-person) of this contact should be recorded in the participant's chart.

The following information can be used as a guideline for you to inform participants verbally with (using plain language):

- *Your last study visit is modified to collect only:*
  - *Adverse events you may have experienced and changes in concomitant medications since last visit*
  - *Any new suicidal ideations or behaviors and measurement of your body weight (except if the visit is performed over the phone)*
- *The decision to terminate treatment in the CNP520 studies was taken in July 2019 after the first observed differences on some cognitive measures between active treatment and placebo groups during a planned review by the independent committee.*
- *The cognitive effect was detected at both Month 3 (Week 13) and Month 6 (Week 26) assessments, in both studies, and at both doses studied in Generation Study 2. Across both studies, more than 80% of participants did not present any remarkable changes in cognition from baseline. Clinical sites do have access to the individual participants' cognitive scores and may discuss them as appropriate.*
- *The objective of the follow-up visit (modified EOS) was to learn more about the time-course of the cognitive findings. This information is now available: no obvious difference in cognitive function was detected between active treatment groups and placebo, when assessments were performed more than 1 month after treatment discontinuation. In other words, the cognitive effects are reversible. Therefore, further measurements at a later time-point are no longer required.*
- *The early time-course for reversal of the cognitive effects is important information that will help developing future prevention therapies for Alzheimer's disease (AD).*
- *Apparent increases in the rate of brain volume loss have also been observed with other amyloid investigational treatments. The changes in brain volume was still detected in the few participants having an MRI scan after washout in this program. There is no direct relationship between decreases in brain volume and cognition. The mechanism for this apparent volume loss still needs to be elucidated.*
- *Body weight loss was more frequent in the participants treated with CNP520 than placebo. If the participant is coming in-person to the site for the study completion visit, an additional weight assessment will be recorded to document body weight after discontinuation of treatment.*
- *If your participant asks which treatment arm they were randomized to, please let them know that this information will be provided to them after formally closing the study database, expected by mid-2020. A summary of study results will also be made available to you for sharing with your participants.*

NOVARTIS

Study participant contact form

(Appendix 4 to Investigator Notification Follow-up #2 - 12 Dec 2019)

Streamlining assessments at the modified End of Study visit for:

☐ [redacted]

☐ Generation Study 2 (CCNP520A2202J)

Information to be stored with trial source data or patients charts.

Participant contacted (Name / Study ID):

Date of contact (dd-mmm-yyyy):	
Means of contact	Phone ☐ In-person ☐
By (Full name, Title, Role):	

Information shared

Results from the interim analysis after treatment discontinuation - Cognitive worsening no longer observed after treatment discontinuation - Body weight loss observed more frequently on treatment than on placebo - Brain volume changes on treatment are deemed related to the mode of action of study medication on brain amyloid	☐ ☐ ☐ (tick as discussed)

mEoS visit requirements

Participant is asked to return for a short safety check as last study visit:	(select planned option)
- Body weight, suicidality risk scale, adverse events and concomitant medications will be collected at site visit	☐
- If participant cannot return, a phone call to collect adverse events and concomitant medications is still required	☐
- Participant has withdrawn from the study and will not return	☐
Date of the mEoS visit (dd-mmm-yyyy) Planned scheduled date: Actual date performed:	