NOVARTIS

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 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 buiten reikwijdte verzoek 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

buiten reikwijdte verzoek

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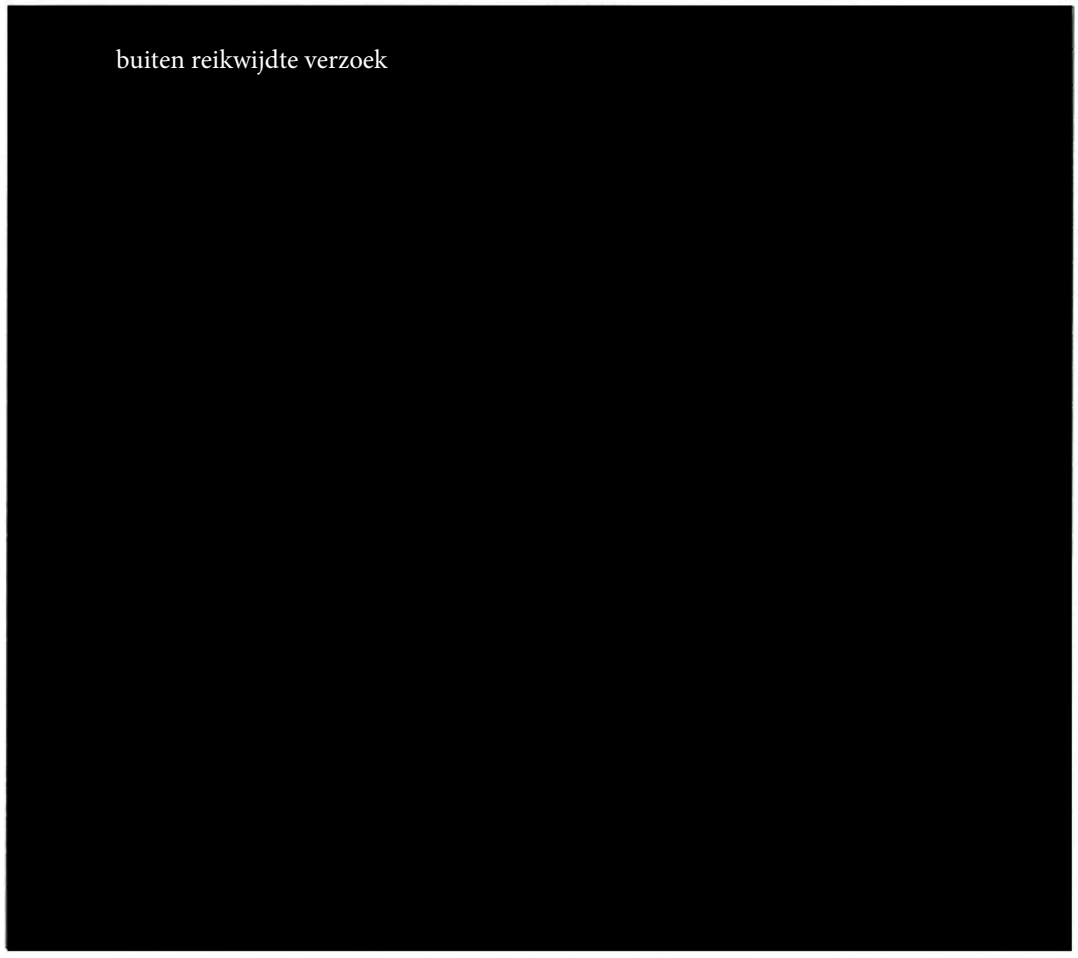

gehele alinea buiten reikwijdte verzoek

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** (± 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