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

Bucharest, 31-May-2021

Subject:	**Notification of Urgent Safety Measures (USM), 27-May-2021, including Temporary halt**
ToetsingOnline dossier no.:	NL68931.100.19
EudraCT no.:	2018-001788-21
Protocol:	CRTH258C2302
Protocol title:	An Eighteen-Month, Two-Arm, Randomized, Double-Masked, Multi center, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Central Retinal Vein Occlusion (RAVEN)
Sponsor:	Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland
EU Legal Rep.:	Novartis Pharma Arzneimittel GmbH, Roonstrasse 25, 90429 Nuernberg, Germany

Dear Madam/Sir,

On behalf of the Sponsor, Parexel International Romania s.r.l. as the applicant herewith notifies **urgent safety measures including Temporary halt as stop of recruitment and stop of treatment** taken for the above referenced clinical trial in response to the increased incidence of Intraocular Inflammation (IOI) and related adverse events including retinal vasculitis (RV), and retinal vascular occlusion (RO) in patients with every 4 weeks dosing beyond the first three doses ("loading phase") in nAMD.

Novartis wishes to inform the authority that following the assessment of the 52-week first interpretable results (FIR) of the clinical study buiten reikwijdte verzoek an increased incidence of IOI and related adverse events including RV, and RO in patients with every 4 weeks (q4 week) dosing beyond the "loading phase" in nAMD) has been observed.

buiten reikwijdte verzoek

- buiten reikwijdte verzoek
- buiten reikwijdte verzoek

[redacted]
buiten reikwijdte verzoek
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buiten reikwijdte verzoek
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Action plan for approved product:

- [redacted]
buiten reikwijdte verzoek
[redacted]
- [redacted]
buiten reikwijdte verzoek
[redacted]

Action plan for clinical trials:

- All the Novartis sponsored RTH258 ongoing clinical studies have been assessed for impact on patient safety of this emerging safety issue, and urgent safety measures (USM) will be initiated for ongoing RTH258 clinical studies in scope (as detailed in the letter to investigators, available upon request).
- Any potential additional relevant measures for clinical studies will be further evaluated and implemented, as appropriate.
- The Investigator's Brochure will be updated to reflect the observed risk of an increased incidence of IOI and related adverse events including RV, and RO in patients with q4 week dosing beyond the "loading phase".

The letter sent by the sponsor to inform the investigators of participating trial sites with full details to this decision is available upon request.

USM requires early termination of the CRTH258C2302 (RAVEN) study, mandating q4 week dosing beyond the "loading phase" for all the patients.

Early termination notification will follow when LPLV is confirmed.
In the meantime, CRTH258C2302 (RAVEN) is on halt as stop of recruitment and stop of treatment for reasons of trial subjects' safety.

No actions are required for any Novartis sponsored brolucizumab clinical studies that do not enable a q4 week dosing beyond the "loading phase".

As of the date of this decision in the Netherlands, 4 subjects are currently enrolled of which 4 subjects are receiving treatment.

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

CCMO numbering	Document	Version/Date
A1	Cover letter	31-May-2021
B5	Substantial Amendment Notification Form	31-May-2021

According to the regulatory requirements of the Netherlands, it is required to submit only the applicable EudraCT forms to support a substantial amendment submission.

The following document is not attached, but is available upon request:

CCMO numbering	Document	Version/Date
K6	Letter to RTH258 Investigators	27-May-2021

With this submission, we declare that all relevant documents of the present submission dossier are signed by the persons authorized for this task

We trust this notification fulfils your requirements; however, in the event of any queries, please do not hesitate to contact us.

Yours faithfully,

Parexel International Romania s.r.l.
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