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

Bucharest, 09-Aug-2021

Subject:	**Declaration of the Local and Global end of trial: Early Termination**
ToetsingOnline dossier no.:	NL68931.100.19
EudraCT no.:	2018-001788-21
Protocol code:	CRTH258C2302
Study title:	An Eighteen-Month, Two-Arm, Randomized, Double- Masked, Multicenter, 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, Basel, 4056, Switzerland
EU Legal Rep	Novartis Pharma Arzneimittel GmbH, Roonstrasse 25, 90429 Nuernberg, Germany

Dear Madam/Sir,

On behalf of the Sponsor **Novartis Pharma AG**, Parexel International Romania s.r .l. herewith notifies the early end of the above referenced clinical trial.

We would like to inform you that Novartis has decided to early terminate the clinical trial and Global Last Patient Last Visit (LPLV) was achieved globally on 26-July-2021

The last subject last visit in The Netherlands occurred on 23-Jun-2021.

This is a premature end of the trial following the notification of urgent safety measure (USM) for the phase III study CRTH258C2302 (RAVEN) evaluating the safety and efficacy of brolucizumab in patients with visual impairment due to retinal vascular occlusion (RVO) compared to aflibercept, as submitted to CCMO on 31st of May 2021. This notification (including the Annex II form) included information on the temporary halt of

the trial to immediately stop enrolment and treatment of patients and the subsequent plan for early termination once premature Last Patient Last Visit (LPLV) is achieved.

Following the assessment of the 52-week first interpretable results (FIR) of the clinical study buiten reikwijdte verzoek, an increased incidence of Intra Ocular Inflammation (IOI) and related adverse events including RV and RO in patients with every 4 weeks (q4 week) dosing beyond the "loading phase" in nAMD subjects has been observed.

Due to the q4 week dosing mandated by studies buiten reikwijdte verzoek and CRTH258C2302 (RAVEN) beyond the loading phase, new safety measures for immediate implementation into the 2 clinical studies prior to IRB/IEC or Health Authority approval have been / are being taken:

- Temporary halt / early termination submitted by 02-Jun-2021 to stop recruitment of new patients and stop treatment of currently enrolled patients in studies buiten reikwijdte verzoek until LPLV of the currently enrolled patients is achieved.
- Early termination of the study will now be implemented, scope of this notification, since LPLV was achieved globally on 26-July-2021

Novartis will proceed with the submission of the clinical trial summary report once available, as required by EU CT-1 guidance (2010/C 82/01) and local regulations.

For Netherlands, the results of this clinical trial will be submitted within the applicable timeline as a separate submission of the clinical trial report (summary) to fulfil national reporting obligations.

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

CCMO numbering	Document	Version/Date
A1	Cover letter	09-Aug-2021
B7	Declaration of the end of trial form-Annex III	09-Aug-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,

Email: 5.1.2.e @Novartis.com

Parexel International Romania s.r.l

5.1.2.e on behalf of 5.1.2.e

5.1.2.e

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