Declaration of the End of Trial Form (cf. Section 4.2.1 of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])

NOTIFICATION OF THE END OF A CLINICAL TRIAL OF A MEDICINE FOR HUMAN USE TO THE COMPETENT AUTHORITY AND THE ETHICS COMMITTEE

For official use

Date of receipt :	Competent authority registration number : Ethics committee registration number:

To be filled in by the applicant

A MEMBER STATE IN WHICH THE DECLARATION IS BEING MADE : The Netherlands

B TRIAL IDENTIFICATION

B.1 EudraCT number :	2018-001788-21
B.2 Sponsor's protocol code number:	CRTH258C2302
B.3 Full title of the trial :	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)

C APPLICANT IDENTIFICATION (please tick the appropriate box)

C.1	**DECLARATION FOR THE COMPETENT AUTHORITY**	☑
C.1.1	Sponsor	☐
C.1.2	Legal representative of the sponsor	☐
C.1.3	Person or organisation authorised by the sponsor to make the application.	☑
C.1.4	**Complete below**:	
C.1.4.1	Organisation : Parexel International Romania s.r.l	
C.1.4.2	Name of person to contact : [redacted]	
C.1.4.3	Address : Metropolis Center, 89-97 Grigore Alexandrescu Street, 010624 Bucharest, Romania	
C.1.4.4	Telephone number : +40 [redacted]	
C.1.4.5	Fax number : +40 [redacted]	
C.1.4.6	E-mail: [redacted]@Novartis.com	

C.2	**DECLARATION FOR THE ETHICS COMMITTEE**	☐
C.2.1	Sponsor	☐
C.2.2	Legal representative of the sponsor	☐
C.2.3	Person or organisation authorised by the sponsor to make the application.	☐
C.2.4	Investigator in charge of the application if applicable[2]:	
	• Co-ordinating investigator (for multicentre trial):	☐
	• Principal investigator (for single centre trial):	☐
C.2.5	**Complete below** :	
C.2.5.1	Organisation:	
C.2.5.2	Name :	
C.2.5.3	Address :	
C.2.5.4	Telephone number :	
C.2.5.5	Fax number :	
C.2.5.6	E-mail :	

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

2 According to national legislation.

D END OF TRIAL

D.1 Date of the end of the trial in this Member State ?[3]	yes ☑ no ☐
D.1.1. (YYYY/MM/DD): 23-Jun-2021	

D.2 Date of the end of the complete trial in all countries concerned by the trial?[3]	yes ☑ no ☐
D.2.1 (YYYY/MM/DD): 2021/07/26	

D.3 Is it an early termination?[4]	yes ☑ no ☐

[3] In case of a multi-country trial, if the national and global end of trial dates are different in a given Member State, the sponsor shall submit this form two times :

1) At the end of the trial in the individual Member State, section D1.1. shall be completed and submitted to the respective National Competent Authority.

2) At the global end of the trial, the sponsor shall complete section D.2.1. with the global trial end date and the completed form shall be submitted to all participating Member States in order to allow the sponsor to prepare the trial result summary within the 12-months (or 6-months in case of paediatric trials) timeframe.

If the national and global end dates coincide in a concerned Member State, the form shall be submitted only once to the National Competent Authority of this Member State with both sections D1.1. and D2.1 complete.

[4] Cf. Section 4.2. of the detailed guidance CT-1.

D.3.1 If yes, give date (YYYY/MM/DD): 2021/07/26
D.3.2 Briefly describe in an annex (free text):
D.3.2.1The justification for early termination of the trial;
Novartis would like to make reference to the notification of the 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 trials 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 and CRTH258C2302 (RAVEN) until LPLV of the currently enrolled patients is achieved.
- Early termination of the studies will now be implemented, scope of this notification, since LPLV was achieved globally on 26-Jul-2021.

D.3.2.2 Number of patients still receiving treatment at time of early termination in the MS concerned by the declaration and their proposed management

Table 0-1 Number of patients still receiving treatment at time of the halt in study CRTH258C2302 (RAVEN)

CRTH258C2302 (RAVEN)	Entire Study	In the MS concerned
Number of subjects receiving treatment	359	4

The proposed management of patients receiving treatment at time of the halt was the following:

- All enrolled (active) subjects were informed as soon as possible about the emerging safety signal leading to studies' early termination and document (subject's chart) that the patient was informed.
- Subjects have been prematurely withdrawn from the study by performing End of study visit (EOS) according to protocol as soon as possible as per protocol requirements.
- After mandatory premature withdrawal the patient may receive standard of care treatment as per investigator's decision.

D.3.2.3 The consequences of early termination for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product.
The temporary halt and the subsequent termination of the study is not expected to impact the evaluation of the safety results and the overall risk benefit assessment, given the number of subjects already enrolled and the characteristics of the observed emerging safety issue.

E SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

E.1 I hereby confirm on behalf of the sponsor that (delete which is not applicable):

- The above information given on this declaration is correct; and
- That the clinical trial summary report will be submitted within the applicable deadlines in accordance with the applicable guidance by the Commission.[5]

E.2 APPLICANT TO THE COMPETENT AUTHORITY (as stated in C.1) ☑

[5] Section 4.3. of the detailed guidance CT-1.

E.2.1 Date : 09-Aug-2021 E.2.2 Signature : E.2.3 Print name: 5.1.2.e on behalf of 5.1.2.e	5.1.2.e	

E.3 APPLICANT TO THE ETHICS COMMITTEE (as stated in C.2) **:**	☐
E.3.1 Date : E.3.2 Signature : E.3.3 Print name:	