To: CCMO - Bevoegde Instantie / Competent Authority[bi@ccmo.nl]
From: [redacted]
Sent: Mon 31-5-2021 15:28:24
Subject: Novartis Pharma AG NL68931.100.19 Notification of Urgent Safety Measures (USM), 27-May-2021, including Temporary halt
Received: Mon 31-5-2021 15:28:38
B5 NL68931.100.19 Substantial Amendment Notif Form 31-May-2021.pdf
A1 NL68931.100.19 Cover Letter USM 31-May-2021.pdf

Dear Madam, Dear Sir,
On behalf of the Sponsor, Novartis Pharma AG, Parexel International Romania s.r.l., herewith submits a substantial amendment to the above-mentioned clinical study for your review and authorization.
The changes in this amendment relate to:

- **Urgent safety measures including Temporary halt as stop of recruitment and stop of treatment**

Please find the following study documents supporting this request for approval attached to this e-mail:

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

We trust that the information provided in the application is sufficient, however if you require any further information, please contact us.
Yours faithfully,

Parexel International Romania s.r.l.
[redacted] on behalf of [redacted]
[redacted]
Metropolis Center
89 -97 Grigore Alexandrescu str
Bucharest, Romania, 010624
Tel: +40 [redacted]
Fax: +40 [redacted]
E-mail: [redacted]@Novartis.com

Substantial Amendment Notification Form (Cf. Section 3.7.b 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 A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

For official use:

Date of receiving the request :	Grounds for non acceptance/ negative opinion : ☐ Date :
Date of start of procedure:	Authorisation/ positive opinion : ☐ Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application ☐ Date :

To be filled in by the applicant:

This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted: THE NETHERLANDS
A.2 Notification for authorisation to the competent authority: ☑
A.3 Notification for an opinion to the ethics committee: ☑

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP?[2] yes ☐ no ☑
B.1.1 If yes repeat this section as necessary.

B.2 Eudract number: 2018-001788-21
B.3 Full title of the trial: 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)
B.4 Sponsor's protocol code number, version, and date: CRTH258C2302, version 01, 8June 2020

B IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1	**Sponsor**
C.1.1	Organisation: Novartis Pharma AG
C.1.2	Name of person to contact: 5.1.2.e
C.1.3	Address: Lichtstrasse 35, 4056 Basel, Switzerland
C.1.4	Telephone number: +41 5.1.2.e
C.1.5	Fax number:
C.1.6	e-mail: 5.1.2.e @novartis.com

C.2	**Legal representative[3] of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)**
C.2.1	Organisation: Novartis Pharma Arzneimittel GmbH
C.2.2	Name of person to contact: 5.1.2.e
C.2.3	Address : Roonstrasse 25; 90429 Nürnberg, Germany
C.2.4	Telephone number : +49 5.1.2.e

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.
2 Cf. Section 3.7. of the detailed guidance CT-1.
3 As stated in Article 19 of Directive 2001/20/EC.

C.2.5	Fax number :
C.2.6	e-mail: [redacted]@novartis.com

D APPLICANT IDENTIFICATION (please tick the appropriate box)

D.1	Request for the competent authority	
D.1.1	Sponsor	☐
D.1.2	Legal representative of the sponsor	☐
D.1.3	Person or organisation authorised by the sponsor to make the application.	☑
D.1.4	Complete below:	
D.1.4.1	Organisation: Parexel International Romania SRL	
D.1.4.2	Name of person to contact: [redacted]	
D.1.4.3	Address: Metropolis Center, 89-97 Grigore Alexandrescu Street, Bucharest, 010624, Romania	
D.1.4.4	Telephone number: +40 [redacted]	
D.1.4.5	Fax number: +40 [redacted]	
D.1.4.6	E-mail: [redacted]@Novartis.com	

D.2	Request for the Ethics Committee	
D.2.1	Sponsor	☐
D.2.2	Legal representative of the sponsor	☐
D.2.3	Person or organisation authorised by the sponsor to make the application.	☐
D.2.4	Investigator in charge of the application if applicable[4]:	
	• Co-ordinating investigator (for multicentre trial)	☐
	• Principal investigator (for single centre trial):	☐
D.2.5	Complete below	
D.2.5.1	Organisation:	
D.2.5.2	Name:	
D.2.5.3	Address:	
D.2.5.4	Telephone number:	
D.2.5.5	Fax number:	
D.2.6	E-mail :	

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1 Sponsor's substantial amendment code number, version, date for the clinical trial concerned:
RTH258 Urgent Safety Measures, 27-May-2021, including Temporary halt affecting study CRTH258C2302

E.2	Type of substantial amendment	
E.2.1	**Amendment to information in the CT application form**	yes ☐ no ☑
E.2.2	**Amendment to the protocol**	yes ☐ no ☑
E.2.3	**Amendment to other documents appended to the initial application form**	yes ☐ no ☑
E.2.3.1	If yes specify:	
E.2.4	**Amendment to other documents or information:**	yes ☐ no ☑
E.2.4.1	If yes specify:	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented[5]**	yes ☑ no ☐
E.2.6	**This amendment is to notify a temporary halt of the trial[6]**	yes ☑ no ☐
E.2.7	**This amendment is to request the restart of the trial[7]**	yes ☐ no ☑

E.3	Reasons for the substantial amendment:

4 According to national legislation.
5 Cf. Section 3.9. of the detailed guidance CT-1.
6 Cf. Section 3.10. of the detailed guidance CT-1.
7 Cf. Section 3.10. of the detailed guidance CT-1.

E.3.1	**Changes in safety or integrity of trial subjects**	**yes** ☑ **no** ☐
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	**yes** ☐ **no** ☑
E.3.3	**Changes in quality of IMP(s)**	**yes** ☐ **no** ☑
E.3.4	**Changes in conduct or management of the trial**	**yes** ☐ **no** ☑
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	**yes** ☐ **no** ☑
E.3.6	**Change/addition of site(s)**	**yes** ☐ **no** ☑
E.3.7	**Other change**	**yes** ☐ **no** ☑
E.3.7.1	**If yes, specify:**	
E.3.8	**Other case**	**yes** ☐ **no** ☑
E.3.8.1	**If yes, specify**	

E.4 Information on temporary halt of tria[8]

E.4.1 **Date of temporary halt** 2021/05/27

E.4.2 **Recruitment has been stopped** yes ☑ no ☐

E.4.3 **Treatment has been stopped** yes ☑ no ☐

E.4.4 Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment

CRTH258C2302: 4

E.4.5 **Briefly describe (free text)**:

- *Justification for a temporary halt of the trial:*

Following the assessment of the 52-week first interpretable results (FIR) of the clinical study [redacted], 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.
Due to the q4 week dosing mandated by studies [redacted] 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 taken (as described in the Dear Investigator Letter available upon request):

- Pause enrolment of new patients into studies [redacted] and CRTH258C2302 (RAVEN) until last patient last visit (LPLV) of the currently enrolled patients is achieved, and early termination of the studies can be implemented.

- *The proposed management of patients receiving treatment at time of the halt :*

- All enrolled subjects must be 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 will be 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.

- *The consequences of the temporary halt 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.

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9] *(free text)*:

Previous and new wording in	New wording	Comments/explanation/reasons for

[8] Cf. Section 3.10. of the detailed guidance CT-1.

[9] Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

track change modus		substantial amendment
As described in the Investigator Letter dated 27-May-2021, available upon request		

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

G.1 Type of change

G.1.1 **Addition of a new site**
G.1.1.1 **Principal investigator** (provide details below)
G.1.1.1.1 Given name
G.1.1.1.2 Middle name (if applicable)
G.1.1.1.3 Family name
G.1.1.1.4 Qualifications (MD……..)
G.1.1.1.5 Professional address
G.1.2 **Removal of an existing site**
G.1.2.1 **Principal investigator** (provide details below)
G.1.2.1.1 Given name
G.1.2.1.2 Middle name (if applicable)
G.1.2.1.3 Family name
G.1.2.1.4 Qualifications (MD……..)
G.1.2.1.5 Professional address
G.1.3 **Change of co-ordinating investigator** (provide details below of the new coordinating investigator)
G.1.3.1 Given name
G.1.3.2 Middle name
G.1.3.3 Family name
G.1.3.4 Qualification (MD…….)
G.1.3.5 Professional address
G.1.3.6 Indicate the name of the previous co-ordinating investigator:
G.1.4 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)
G.1.4.1 Given name
G.1.4.2 Middle name
G.1.4.3 Family name
G.1.4.4 Qualifications (MD……..)
G.1.4.5 Professional address
G.1.4.6 Indicate the name of the previous principal investigator:

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

H.1 Change of e-mail contact for feedback on application*

H.2 Change to request to receive an .xml copy of CTA data ☐ yes ☐ no
H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ☐ yes ☐ no
H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):
H.2.2 Do you want to receive this via password protected link(s)[10]? ☐ yes ☐ no

If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)

H.2.3 Do you want to stop messages to an email for which they were previously requested? ☐ yes ☐ no
H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:

(*This will only come into effect from the time at which the request is processed in EudraCT).

I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

[10] This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

I.1	**Cover letter**	☑
I.2	**Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)**	☐
I.3	**Entire new version of the document**[11]	☐
I.4	**Supporting information (Investigator letter)**	**HA**☐**EC**☑
I.5	**Revised .xml file and copy of initial application form with amended data highlighted**	☐
I.6	**Comments on any novel aspect of the amendment if any :**	

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

J.1 I hereby ~~confirm that~~/ confirm on behalf of the sponsor that (delete which is not applicable)

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY(as stated in section D.1): ☑

J.2.1 Signature [12]:
J.2.2 Print name : 5.1.2.e on behalf of 5.1.2.e 5.1.2.e
J.2.3 Date : 31-May-2021

J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section D.2): ☐

J.3.1 Signature [13]:
J.3.2 Print name:
J.3.3 Date :

[11] Cf. Section 3.7.c. of the detailed guidance CT-1.
[12] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
[13] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.

Parexel International Romania s.r.l.
Metropolis Center - Str. Grigore Alexandrescu, Nr.89-97,
Sector 1, 010624 Bucharest, Romania
J40/9291 /2004; CUI: RO 16494261
Phone: +40 5.1.2.e
Fax: +40 5.1.2.e
www.parexel.com

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

buiten reikwijdte verzoek

buiten reikwijdte verzoek

buiten reikwijdte verzoek

buiten reikwijdte verzoek

Action plan for approved product:

- buiten reikwijdte verzoek

buiten reikwijdte verzoek

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.
5.1.2.e **on behalf of** 5.1.2.e
5.1.2.e
Metropolis Center
89 -97 Grigore Alexandrescu str
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