

To: CCMO - Bevoegde Instantie / Competent Authority[bi@ccmo.nl]
From: 5.1.2.e, 5.1.2.e (Ext)
Sent: Mon 10-5-2021 11:08:48
Subject: NL71107.056.19_EudraCT 2018-004233-33_Novartis Protocol CMHS552A12101 - Temporary Halt
Received: Mon 10-5-2021 11:09:03
[A1 CMHS552A12101 Cover letter to CA NL71107.056.19_10May21.pdf](#)
[B5 CMHS552A1201 Substantial amendment notification form temphalt_10May21.pdf](#)

Dear Madam/Sir,

On behalf of the Sponsor, Novartis Pharma AG, Parexel International Romania s.r.l. herewith submits a substantial amendment for the above referenced clinical trial for review and authorization.

The substantial amendment consists of:

- Temporary halt of the trial starting 07-May-2021

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

Yours faithfully,

5.1.2.e

Novartis CTA HUB

Metropolis Center, Str. Grigore Alexandrescu, No. 89-97, Bucharest, Romania, 010624

Tel: +40 5.1.2.e

Fax: +40 5.1.2.e

Email: 5.1.2.e [@Novartis.com](#)

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

Bucharest, Date: 10 May 2021

**Subject: Digital submission of a substantial amendment for approval:
Temporary halt of the trial**

EudraCT no.: 2018-004233-33

Novartis study no.: CMHS552A12101

ToetsingOnline **NL71107.056.19**

Dossier no.:

Study title: A first-in-human, randomized, subject-blinded, placebo-controlled, single ascending dose study to investigate the safety, tolerability and pharmacokinetics of MHS552 in healthy volunteers

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 trial for review and authorization.

The changes in this amendment relate to:

- Temporary halt of the trial starting 07-May-2021

Two subjects in this FIH study experienced hypersensitivity-like reactions assessed as CTCAE AEs grade 2 or higher that were considered drug-related and therefore study-stopping rules were met as agreed by both the Investigator and Sponsor. Enrollment is placed on hold. A full safety review will be conducted.

No patients are in active treatment, 60 have been treated: 40 having completed the study, 20 remain in follow-up.

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

CCMO numbering	Document	Version/Date
A1	Cover letter	10-May-2021
B5	EudraCT Annex 2 form for amendments	10-May-2021

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

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

Yours faithfully,

5.1.2.e

Parexel International Romania SRL

5.1.2.e

Metropolis Center, Str. Grigore Alexandrescu, No. 89-97
Bucharest, 010624, Romania
Tel.: +40 5.1.2.e
Fax: +40 5.1.2.e
E-mail: 5.1.2.e@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 : <input type="checkbox"/> Date :
Date of start of procedure:	Authorisation/ positive opinion : <input type="checkbox"/> Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application <input type="checkbox"/> 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	<input checked="" type="checkbox"/>
A.2 Notification for authorisation to the competent authority:	<input checked="" type="checkbox"/>
A.3 Notification for an opinion to the ethics committee:	<input checked="" type="checkbox"/>

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 <input type="checkbox"/> no <input checked="" type="checkbox"/>
B.1.1 If yes repeat this section as necessary.

B.2 Eudract number: 2018-004233-33
B.3 Full title of the trial : A first-in-human, randomized, subject-blinded, placebo-controlled, single ascending dose study to investigate the safety, tolerability and pharmacokinetics of MHS552 in healthy volunteers
B.4 Sponsor's protocol code number, version, and date: CMHS552A12101, v02, 28Jul2020

C 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: Lichtstr. 35, Basel 4056, Switzerland
C.1.4 Telephone number : 001 5.1.2.e
C.1.5 Fax number : 001 5.1.2.e
C.1.6 e-mail: 5.1.2.e @novartis.com

C.2 Legal representative³ 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
C.2.5 Fax number : +49-(5.1.2.e
C.2.6 e-mail: 5.1.2.e @novartis.com

D APPLICANT IDENTIFICATION (please tick the appropriate box)

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.

D.1 Request for the competent authority	
D.1.1 Sponsor	<input type="checkbox"/>
D.1.2 Legal representative of the sponsor	<input type="checkbox"/>
D.1.3 Person or organisation authorised by the sponsor to make the application.	<input checked="" type="checkbox"/>
D.1.4 Complete below:	
D.1.4.1 Organisation : Parexel International Romania s.r.l.	
D.1.4.2 Name of person to contact : 5.1.2.e	
D.1.4.3 Address : Metropolis Center, 89-97 Grigore Alexandrescu St., 010624 Bucharest, Romania	
D.1.4.4 Telephone number : +40 5.1.2.e	
D.1.4.5 Fax number : +40 5.1.2.e	
D.1.4.6 E-mail: 5.1.2.e @novartis.com	

D.2 Request for the Ethics Committee	
D.2.1 Sponsor	<input type="checkbox"/>
D.2.2 Legal representative of the sponsor	<input type="checkbox"/>
D.2.3 Person or organisation authorised by the sponsor to make the application.	<input type="checkbox"/>
D.2.4 Investigator in charge of the application if applicable ⁴ :	
• Co-ordinating investigator (for multicentre trial)	<input type="checkbox"/>
• Principal investigator (for single centre trial):	<input type="checkbox"/>
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: Temporary halt in CMHS552A12101 FIH study
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E.2 Type of substantial amendment	
E.2.1 Amendment to information in the CT application form	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.2 Amendment to the protocol	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.3 Amendment to other documents appended to the initial application form	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.3.1 If yes specify:	
E.2.4 Amendment to other documents or information:	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.4.1 If yes specify:	
E.2.5 This amendment concerns mainly urgent safety measures already implemented ⁵	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.2.6 This amendment is to notify a temporary halt of the trial ⁶	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.2.7 This amendment is to request the restart of the trial ⁷	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>

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 Reasons for the substantial amendment:		
E.3.1	Changes in safety or integrity of trial subjects	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.2	Changes in interpretation of scientific documents/value of the trial	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.3	Changes in quality of IMP(s)	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.4	Changes in conduct or management of the trial	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.5	Change or addition of principal investigator(s), co-ordinating investigator	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.6	Change/addition of site(s)	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.7	Other change	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
E.3.7.1	If yes, specify:	
E.3.8	Other case	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.3.8.1	If yes, specify Temporary halt of the trial	

E.4 Information on temporary halt of trial⁸		
E.4.1	Date of temporary halt (YYYY/MM/DD)	2021/05/07
E.4.2	Recruitment has been stopped	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.4.3	Treatment has been stopped	yes <input checked="" type="checkbox"/> no <input type="checkbox"/>
E.4.4	Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment: 0 (None in active treatment, 60 have been treated: 40 having completed the study, 20 remain in follow-up)	
E.4.5	Briefly describe (free text): <ul style="list-style-type: none"> Justification for a temporary halt of the trial The proposed management of patients receiving treatment at time of the halt (<i>free text</i>). The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product (<i>free text</i>). <p>Two subjects in the FIH study experienced hypersensitivity-like reactions assessed as CTCAE AEs grade 2 or higher that were considered drug-related and therefore study-stopping rules were met as agreed by both the Investigator and Sponsor. Enrolment is placed on hold. A full safety review will be conducted.</p>	

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT⁹ (*free text*): N/A

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment

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

G.1 Type of change

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.

- 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)

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 document¹¹**

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

- I.4 Supporting information**
- 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:

5.1.2.e

J.2.2 Print name :

5.1.2.e

J.2.3 Date : 10-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.