

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>). 	
	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.	

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.