REPOTRIAL

An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777111.

Deliverable
D3.8 "Publication on study design, study protocol and start: pilot study 2 (TBD)"

Work Package
WP3 "Clinical validation of in-silico trial prediction"

Disclaimer

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Document information

Grant Agreement Number: 777111				**Acronym: REPO-TRIAL**
Full title	An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes			
Topic	In-silico trials for developing and assessing biomedical products			
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Project Coordinator	Prof. Dr. Harald H.H.W. Schmidt, Universiteit Maastricht (UM)			
Deliverable	D3.8			
Work Package	WP3			
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History of changes

Version	Date	Contributions	Contributors (name and institution)
V0.1	17/11/2023	First draft	Harald Schmidt (UM), Vanessa Köhler (concentris)
V1	17/11/2023	Final version	Harald Schmidt (UM)
V1	18/11/2023	Approval	Harald Schmidt (UM)
V1	20/11/2023	Submission	Vanessa Köhler (concentris)

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Table of Content

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1 Objectives of the deliverable based on the Description of Action (DoA)

This deliverable report contains the study details (Clinical trial Application Forms) of the

- REPO-HFpEF I study (full title - “Clinical safety evaluation in healthy volunteers of REPurposed citrulline and fOlic acid in combination with vericiguat as a possible treatment in Heart Failure with Preserved Ejection Fraction”)

- and REPO-HFpEF II study (full title - “Mechanism-based drug REpurPOsing in a subtype of Heart Failure with Preserved Ejection Fraction (REPO-HFPEF)” as attachment.

Both trials have been uploaded to the EudraCT platform.

2 Attachment

- Clinical trial Application Form - “Clinical safety evaluation in healthy volunteers of REPurposed citrulline and fOlic acid in combination with vericiguat as a possible treatment in Heart Failure with Preserved Ejection Fraction” (REPO-HFpEF I)
- Clinical trial Application Form - “Mechanism-based drug REpurPOsing in a subtype of Heart Failure with Preserved Ejection Fraction (REPO-HFPEF)” (REPO-HFpEF II)

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Annex 1: Clinical trial Application Form

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

To be filled in by the applicant
The questions in this form for the request for authorisation from the Competent Authority are also relevant for the opinion from an Ethics Committee (it represents module 1 of the form for applying to an ethics committee) and can be used as part of that application. Please indicate the relevant purpose in a box below.

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: Yes ●
REQUEST FOR OPINION OF THE ETHICS COMMITTEE: No ●

A. TRIAL IDENTIFICATION

A.1	Member State in which the submission is being made:	**Germany - BfArM**
A.2	EudraCT number:	**2021-005028-39**
A.3	Full title of the trial:	
	English	**Clinical safety evaluation in healthy volunteers of REPurposed citrulline and fOlic acid in combination with vericiguat as a possible treatment in Heart Failure with Preserved Ejection Fraction**
A.3.1	Title of the trial for lay people, in easily understood, i.e. non-technical, language:	
	English	**Combined administration of citrulline, folic acid and vericugat in healthy subjects to assess clinical safety in regard to a treatment of patients with heart failure in the future**
A.3.2	Name or abbreviated title of the trial where available:	
	English	**REPO-HFpEF I**
A.4	Sponsor's protocol code number, version and date[1]:	
A.4.1	Sponsor's protocol code number:	**Ph1U_EXT-202001**
A.4.2	Sponsor's protocol version:	**2.0**
A.4.3	Sponsor's protocol date:	**2021-11-25**
A.5	Additional international study identifiers (e.g. WHO, ISRCTN[2] , US NCT Number[3]) if available	
A.5.1	ISRCTN number:	
A.5.2	US NCT number:	
A.5.3	WHO Universal Trial Number (UTN):	
A.5.4	Other Identifier:	
A.6	Is this a resubmission?	**No ●**
	If 'Yes', indicate the resubmission letter[4]:	**First Submission**
A.7	Is the trial part of an agreed Paediatric Investigation Plan?	**No ●**
A.8	EMA Decision number of Paediatric Investigation Plan:	

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B.1	**SPONSOR**	
B.1.1	Name of organisation:	**Maastricht University**
B.1.2	Name of the person to contact:	
B.1.2.1	Given name	**Harald**
B.1.2.2	Middle name	
B.1.2.3	Family name	**Schmidt**
B.1.3	Address:	
B.1.3.1	Street address	**Universiteitssingel 40**
B.1.3.2	Town/city	**Maastricht**
B.1.3.3	Post code	**6229**
B.1.3.4	Country	**Netherlands**
B.1.4	Telephone number:	
B.1.5	Fax number:	
B.1.6	E-mail:	**hschmidt@ppmlab.net**

B.2	**LEGAL REPRESENTATIVE[5] OF THE SPONSOR IN THE COMMUNITY FOR THE PURPOSE OF THIS TRIAL** (if different from the sponsor)
B.2.1	Name of organisation:
B.2.2	Name of person to contact:
B.2.2.1	Given name
B.2.2.2	Middle name
B.2.2.3	Family name
B.2.3	Address:
B.2.3.1	Street address
B.2.3.2	Town/city
B.2.3.3	Post code
B.2.3.4	Country
B.2.4	Telephone number:
B.2.5	Fax number:
B.2.6	E-mail:

B.3	**STATUS OF THE SPONSOR:**	
B.3.1	Commercial:	**No •**
B.3.2	Non commercial:	**Yes •**

B.4	**Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):**	
B.4.1	Name of organisation:	**EU Commission**
B.4.2	Country:	**Belgium**

B.5	**Contact point[6] designated by the sponsor for further information on the trial**	
B.5.1	Name of organisation:	**University Hospital Bonn**
B.5.2	Functional name of contact point (e.g. "Clinical Trial Information Desk"):	**Studienzentrale (SZB)**
B.5.3	Address:	
B.5.3.1	Street address	**Venusberg-Campus 1**
B.5.3.2	Town/city	**Bonn**
B.5.3.3	Post code	**53227**
B.5.3.4	Country	**Germany**
B.5.4	Telephone number:	
B.5.5	Fax number:	
B.5.6	E-mail: (use a functional e-mail address rather than a personal one)	**studienzentrale-szb@ukbonn.de**

C. APPLICANT IDENTIFICATION, (please tick the appropriate box)

C.1	REQUEST 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	**Yes •**
C.1.4	Complete the details of the applicant below even if they are provided elsewhere on the form:	
C.1.4.1	Name of Organisation:	**Studienzentrale (SZB), University Hospital Bonn**
C.1.4.2	Name of contact person:	
C.1.4.2.1	Given name	**Corinna**
C.1.4.2.2	Middle name	
C.1.4.2.3	Family name	**Reineke**
C.1.4.3	Address:	
C.1.4.3.1	Street address	**Venusberg-Campus 1**
C.1.4.3.2	Town/city	**Bonn**
C.1.4.3.3	Post code	**53227**
C.1.4.3.4	Country	**Germany**
C.1.4.4	Telephone number:	
C.1.4.5	Fax number:	**+49 228 2871 6039**
C.1.4.6	E-mail:	**corinna.reineke@ukbonn.de**
C.1.5	Request to receive a copy of CTA data as XML:	
C.1.5.1	Do you want a copy of the CTA form data saved on EudraCT as an XML file?	**Yes •**
C.1.5.1.1	If Yes provide the e-mail address(es) to which it should be sent (up to 5 addresses): **corinna.reineke@ukbonn.de**	
C.1.5.1.2	Do you want to receive this via password protected link(s)[7]?	**Yes •**

If you answer No to question C.1.5.1.2 the .xml file will be transmitted by less secure e-mail link(s)

D. INFORMATION ON EACH IMP

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator and each placebo, if applicable. ***For placebo go directly to D.8****. If the trial is performed with several products use extra pages and give each product a sequential number in D.1.1. If the product is a combination product, information should be given for each active substance.*

D.1	**IMP IDENTIFICATION**	
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	**PR1**
D.1.2	IMP being tested	**Yes •**
D.1.3	IMP used as a comparator	**No •**

D.2	**STATUS OF THE IMP**	
D.2.1	Has the IMP to be used in the trial a marketing authorisation?	**Yes •**
If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.		
D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name **Folsan**	
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	**Teofarma SRL**
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	**9185.00.00**
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation?	**Yes •**
D.2.1.1.4.1	If 'Yes', please specify: **study specific labeling**	
D.2.1.2	The country that granted the Marketing Authorisation	**Germany**
D.2.1.2.1	Is this the Member State concerned with this application?	**Yes •**

D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active substance?	**No •**
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?	**No •**
D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group[9]	**Yes •**
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other:	**No •**
D.2.2.4.1	If 'Yes', please specify:	

D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD:	**No •**
D.2.3.2	Simplified IMPD:	**Yes •**
D.2.3.3	Summary of product characteristics (SmPC) only:	**No •**
D.2.4	Has the use of the IMP been previously authorised in a	**No •**

	clinical trial conducted by the sponsor in the Community?	
D.2.4.1	If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	**No •**
D.2.5.1	If 'Yes', give the orphan drug designation number[10]**:**	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	**Yes •**
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP[11]?	**No •**
D.2.6.1.2	National Competent Authority?	**Yes •**

D.3	**DESCRIPTION OF THE IMP**	
D.3.1	Product name where applicable[12]:	**Folsan**
D.3.2	Product code where applicable[13]:	
D.3.3	ATC codes, if officially registered[14]:	**B03B**
D.3.4	Pharmaceutical form (use standard terms):	**Tablet**
D.3.4.1	Is this a specific paediatric formulation?	**No •**
D.3.5	Maximum duration of treatment of a subject according to the protocol: **12 days**	
D.3.6	Dose allowed:	
D.3.6.1	For first trial only:	
	Specify per day or total	**Not Answered •**
	Specify total dose (number and unit):	
	Route of administration (relevant to the first dose):	
D.3.6.2	For all trials	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	**60 mg milligram(s)**
	Route of administration (relevant to the maximum dose):	**Oral use**
D.3.7	Routes of administration (use standard terms):	**Oral use**

D.3.8	Name of each active substance (INN or proposed INN if available): **Folic acid**	
D.3.9	Other available name for each active substance (provide all available):	
D.3.9.1	CAS[15] number	
D.3.9.2	Current sponsor code	
D.3.9.3	Other descriptive name **FOLIC ACID**	
D.3.9.4	EV Substance code	**SUB07774MIG**
D.3.9.5	Full Molecular formula	
D.3.9.6	Chemical/biological description of the Active Substance	
D.3.10	Strength (specify all strengths to be used):	
D.3.10.1	Concentration unit:	**mg milligram(s)**
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):	**equal**
D.3.10.3	Concentration (number).	**5**

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	**Yes •**
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP)?	**No •**
Is this a:		

D.3.11.3	Advanced Therapy IMP (ATIMP)?	**No** •
D.3.11.3.1	Somatic cell therapy medicinal product[16]?	**No** •
D.3.11.3.2	Gene therapy medicinal product[17]?	**No** •
D.3.11.3.3	Tissue Engineered Product[18]?	**No** •
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device[19])?	**No** •
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	**No** •
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	**No** •
D.3.11.5	Radiopharmaceutical medicinal product?	**No** •
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	**No** •
D.3.11.7	Plasma derived medicinal product?	**No** •
D.3.11.8	Extractive medicinal product?	**No** •
D.3.11.9	Recombinant medicinal product?	**No** •
D.3.11.10	Medicinal product containing genetically modified organisms?	**No** •
D.3.11.10.1	Has the authorisation for contained use or release been granted?	**No** •
D.3.11.10.2	Is it pending?	**No** •
D.3.11.11	Herbal medicinal product?	**No** •
D.3.11.12	Homeopathic medicinal product?	**No** •
D.3.11.13	Another type of medicinal product?	**No** •
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	
D.3.12	Mode of action (*free text*[20])	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	**No** •
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH?[21]	

D.4	**SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)**	
D.4.1	Origin of cells	
D.4.1.1	Autologous	**No** •
D.4.1.2	Allogeneic	**No** •
D.4.1.3	Xenogeneic	**No** •
D.4.1.3.1	If 'Yes', specify the species of origin:	
D.4.2	Type of cells	
D.4.2.1	Stem cells	**No** •
D.4.2.2	Differentiated cells	**No** •
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes…):	
D.4.2.3	Others:	**No** •
D.4.2.3.1	If others, specify:	

D.5	**GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS**	
D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	**No** •
D.5.3	Ex vivo gene therapy:	**No** •
D.5.4	Type of gene transfer product	
D.5.4.1	Nucleic acid (e.g. plasmid): If 'Yes', specify if:	**No** •
D.5.4.1.1	Naked:	**No** •
D.5.4.1.2	Complexed	**No** •
D.5.4.2	Viral vector:	**No** •

D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, …:	
D.5.4.3	Others	**No •**
D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells:	**No •**
If 'Yes', specify the origin of the cells:		
D.5.5.1	Autologous:	**No •**
D.5.5.2	Allogeneic:	**No •**
D.5.5.3	Xenogeneic:	**No •**
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells…):	

D.6	**TISSUE ENGINEERED PRODUCT**	
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.		
D.6.1	Origin of cells	
D.6.1.1	Autologous	**No •**
D.6.1.2	Allogeneic	**No •**
D.6.1.3	Xenogeneic	**No •**
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	**No •**
D.6.2.2	Differentiated cells	**No •**
D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, …):	
D.6.2.3	Others:	**No •**
D.6.2.3.1	If others, specify:	

D.7	**PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)**	
D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	**No •**
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	**No •**
D.7.4.1.1	Does this medical device have a CE mark?	**No •**
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	**No •**
D.7.4.3	Scaffolds?	**No •**
D.7.4.4	Matrices?	**No •**
D.7.4.5	Other?	**No •**
D.7.4.5.1	If other, specify:	

D.1	**IMP IDENTIFICATION**	
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	**PR2**
D.1.2	IMP being tested	**Yes •**
D.1.3	IMP used as a comparator	**No •**

D.2	**STATUS OF THE IMP**	
D.2.1	Has the IMP to be used in the trial a marketing authorisation?	**Yes •**

If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.

D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name **Stimol**	
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	**BIOCODEX**
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	**3400933452025**
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation?	**Yes •**
D.2.1.1.4.1	If 'Yes', please specify: **study specific labeling**	
D.2.1.2	The country that granted the Marketing Authorisation	**France**
D.2.1.2.1	Is this the Member State concerned with this application?	**No •**

D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active substance?	**No •**
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?	**No •**
D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group[9]	**Yes •**
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other:	**No •**
D.2.2.4.1	If 'Yes', please specify:	

D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD:	**No •**
D.2.3.2	Simplified IMPD:	**Yes •**
D.2.3.3	Summary of product characteristics (SmPC) only:	**No •**
D.2.4	Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?	**No •**
D.2.4.1	If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	**No •**
D.2.5.1	If 'Yes', give the orphan drug designation number[10]**:**	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	**Yes •**
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP[11]?	**No •**
D.2.6.1.2	National Competent Authority?	**Yes •**

D.3	**DESCRIPTION OF THE IMP**	
D.3.1	Product name where applicable[12]:	
D.3.2	Product code where applicable[13]:	
D.3.3	ATC codes, if officially registered[14]:	**V06DD**
D.3.4	Pharmaceutical form (use standard terms):	**Solution for use in drinking water**

D.3.4.1	Is this a specific paediatric formulation?	**No •**
D.3.5	Maximum duration of treatment of a subject according to the protocol: **12 days**	
D.3.6	Dose allowed:	
D.3.6.1	For first trial only:	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	
	Route of administration (relevant to the first dose):	
D.3.6.2	For all trials	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	**72 g gram(s)**
	Route of administration (relevant to the maximum dose):	**Oral use**
D.3.7	Routes of administration (use standard terms):	**Oral use**

D.3.8	Name of each active substance (INN or proposed INN if available): **Citrulline Malate**	
D.3.9	Other available name for each active substance (provide all available):	
D.3.9.1	CAS[15] number	**70796-17-7**
D.3.9.2	Current sponsor code	
D.3.9.3	Other descriptive name **CITRULLINE MALATE**	
D.3.9.4	EV Substance code	**SUB13385MIG**
D.3.9.5	Full Molecular formula	
D.3.9.6	Chemical/biological description of the Active Substance	
D.3.10	Strength (specify all strengths to be used):	
D.3.10.1	Concentration unit:	**g gram(s)**
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):	**equal**
D.3.10.3	Concentration (number).	**1**

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	**Yes •**
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP)?	**No •**
Is this a:		
D.3.11.3	Advanced Therapy IMP (ATIMP)?	**No •**
D.3.11.3.1	Somatic cell therapy medicinal product[16]?	**No •**
D.3.11.3.2	Gene therapy medicinal product[17]?	**No •**
D.3.11.3.3	Tissue Engineered Product[18]?	**No •**
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device[19])?	**No •**
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	**No •**
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	**No •**
D.3.11.5	Radiopharmaceutical medicinal product?	**No •**
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	**No •**
D.3.11.7	Plasma derived medicinal product?	**No •**
D.3.11.8	Extractive medicinal product?	**No •**
D.3.11.9	Recombinant medicinal product?	**No •**
D.3.11.10	Medicinal product containing genetically modified organisms?	**No •**
D.3.11.10.1	Has the authorisation for contained use or release	**No •**

	been granted?	
D.3.11.10.2	Is it pending?	**No** •
D.3.11.11	Herbal medicinal product?	**No** •
D.3.11.12	Homeopathic medicinal product?	**No** •
D.3.11.13	Another type of medicinal product?	**No** •
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	
D.3.12	Mode of action (*free text*[20])	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	**No** •
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH?[21]	

D.4	**SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)**	
D.4.1	Origin of cells	
D.4.1.1	Autologous	**No** •
D.4.1.2	Allogeneic	**No** •
D.4.1.3	Xenogeneic	**No** •
D.4.1.3.1	If 'Yes', specify the species of origin:	
D.4.2	Type of cells	
D.4.2.1	Stem cells	**No** •
D.4.2.2	Differentiated cells	**No** •
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes…):	
D.4.2.3	Others:	**No** •
D.4.2.3.1	If others, specify:	

D.5	**GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS**	
D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	**No** •
D.5.3	Ex vivo gene therapy:	**No** •
D.5.4	Type of gene transfer product	
D.5.4.1	Nucleic acid (e.g. plasmid):	**No** •
	If 'Yes', specify if:	
D.5.4.1.1	Naked:	**No** •
D.5.4.1.2	Complexed	**No** •
D.5.4.2	Viral vector:	**No** •
D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, …:	
D.5.4.3	Others	**No** •
D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells:	**No** •
If 'Yes', specify the origin of the cells:		
D.5.5.1	Autologous:	**No** •
D.5.5.2	Allogeneic:	**No** •
D.5.5.3	Xenogeneic:	**No** •
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells…):	

D.6	**TISSUE ENGINEERED PRODUCT**	
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.		
D.6.1	Origin of cells	
D.6.1.1	Autologous	**No** •
D.6.1.2	Allogeneic	**No** •

D.6.1.3	Xenogeneic	**No •**
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	**No •**
D.6.2.2	Differentiated cells	**No •**
D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, …):	
D.6.2.3	Others:	**No •**
D.6.2.3.1	If others, specify:	

D.7	**PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)**	
D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	**No •**
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	**No •**
D.7.4.1.1	Does this medical device have a CE mark?	**No •**
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	**No •**
D.7.4.3	Scaffolds?	**No •**
D.7.4.4	Matrices?	**No •**
D.7.4.5	Other?	**No •**
D.7.4.5.1	If other, specify:	

D.1	**IMP IDENTIFICATION**	
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	**PR3**
D.1.2	IMP being tested	**Yes •**
D.1.3	IMP used as a comparator	**No •**

D.2	**STATUS OF THE IMP**	
D.2.1	Has the IMP to be used in the trial a marketing authorisation?	**Yes •**
If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.		
D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name **Verquvo 10mg Filmtabletten**	
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	**Bayer AG**
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	**EU/1/21/1561/026**
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation?	**Yes •**
D.2.1.1.4.1	If 'Yes', please specify: **study specific labeling**	
D.2.1.2	The country that granted the Marketing Authorisation	**Germany**
D.2.1.2.1	Is this the Member State concerned with this application?	**Yes •**

D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active	**No •**

	substance?	
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?	**No •**
D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group[9]	**Yes •**
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other:	**No •**
D.2.2.4.1	If 'Yes', please specify:	

D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD:	**No •**
D.2.3.2	Simplified IMPD:	**Yes •**
D.2.3.3	Summary of product characteristics (SmPC) only:	**No •**
D.2.4	Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?	**No •**
D.2.4.1	If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	**No •**
D.2.5.1	If 'Yes', give the orphan drug designation number[10]**:**	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	**Yes •**
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP[11]?	**No •**
D.2.6.1.2	National Competent Authority?	**Yes •**

D.3	**DESCRIPTION OF THE IMP**	
D.3.1	Product name where applicable[12]:	
D.3.2	Product code where applicable[13]:	
D.3.3	ATC codes, if officially registered[14]:	**C01DX22**
D.3.4	Pharmaceutical form (use standard terms):	
D.3.4.1	Is this a specific paediatric formulation?	**No •**
D.3.5	Maximum duration of treatment of a subject according to the protocol:	
D.3.6	Dose allowed:	
D.3.6.1	For first trial only:	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	
	Route of administration (relevant to the first dose):	
D.3.6.2	For all trials	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	**60 mg milligram(s)**
	Route of administration (relevant to the maximum dose):	**Oral use**
D.3.7	Routes of administration (use standard terms):	**Oral use**

D.3.8	Name of each active substance (INN or proposed INN if available): **Vericiguat**
D.3.9	Other available name for each active substance (provide all available):
D.3.9.1	CAS[15] number
D.3.9.2	Current sponsor code

D.3.9.3	Other descriptive name **Vericiguat**	
D.3.9.4	EV Substance code	**SUB189401**
D.3.9.5	Full Molecular formula	
D.3.9.6	Chemical/biological description of the Active Substance	
D.3.10	Strength (specify all strengths to be used):	
D.3.10.1	Concentration unit:	**mg milligram(s)**
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):	**equal**
D.3.10.3	Concentration (number).	**10**

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	**Yes •**
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP)?	**No •**
Is this a:		
D.3.11.3	Advanced Therapy IMP (ATIMP)?	**No •**
D.3.11.3.1	Somatic cell therapy medicinal product[16]?	**No •**
D.3.11.3.2	Gene therapy medicinal product[17]?	**No •**
D.3.11.3.3	Tissue Engineered Product[18]?	**No •**
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device[19])?	**No •**
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	**No •**
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	**No •**
D.3.11.5	Radiopharmaceutical medicinal product?	**No •**
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	**No •**
D.3.11.7	Plasma derived medicinal product?	**No •**
D.3.11.8	Extractive medicinal product?	**No •**
D.3.11.9	Recombinant medicinal product?	**No •**
D.3.11.10	Medicinal product containing genetically modified organisms?	**No •**
D.3.11.10.1	Has the authorisation for contained use or release been granted?	**No •**
D.3.11.10.2	Is it pending?	**No •**
D.3.11.11	Herbal medicinal product?	**No •**
D.3.11.12	Homeopathic medicinal product?	**No •**
D.3.11.13	Another type of medicinal product?	**No •**
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	
D.3.12	Mode of action (*free text*[20])	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	**No •**
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH?[21]	

D.4	**SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)**	
D.4.1	Origin of cells	
D.4.1.1	Autologous	**No •**
D.4.1.2	Allogeneic	**No •**
D.4.1.3	Xenogeneic	**No •**
D.4.1.3.1	If 'Yes', specify the species of origin:	

D.4.2	Type of cells	
D.4.2.1	Stem cells	**No** •
D.4.2.2	Differentiated cells	**No** •
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes…):	
D.4.2.3	Others:	**No** •
D.4.2.3.1	If others, specify:	

D.5	**GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS**	
D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	**No** •
D.5.3	Ex vivo gene therapy:	**No** •
D.5.4	Type of gene transfer product	
D.5.4.1	Nucleic acid (e.g. plasmid):	**No** •
	If 'Yes', specify if:	
D.5.4.1.1	Naked:	**No** •
D.5.4.1.2	Complexed	**No** •
D.5.4.2	Viral vector:	**No** •
D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, …:	
D.5.4.3	Others	**No** •
D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells:	**No** •
If 'Yes', specify the origin of the cells:		
D.5.5.1	Autologous:	**No** •
D.5.5.2	Allogeneic:	**No** •
D.5.5.3	Xenogeneic:	**No** •
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells…):	

D.6	**TISSUE ENGINEERED PRODUCT**	
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.		
D.6.1	Origin of cells	
D.6.1.1	Autologous	**No** •
D.6.1.2	Allogeneic	**No** •
D.6.1.3	Xenogeneic	**No** •
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	**No** •
D.6.2.2	Differentiated cells	**No** •
D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, …):	
D.6.2.3	Others:	**No** •
D.6.2.3.1	If others, specify:	

D.7	PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)	
D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	**No •**
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	**No •**
D.7.4.1.1	Does this medical device have a CE mark?	**No •**
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	**No •**
D.7.4.3	Scaffolds?	**No •**
D.7.4.4	Matrices?	**No •**
D.7.4.5	Other?	**No •**
D.7.4.5.1	If other, specify:	

D.8 INFORMATION ON PLACEBO (if relevant; repeat as necessary)

D.8.1	Is there a placebo:	**No •**

D.8.2	This refers to placebo number:	
D.8.3	Pharmaceutical form:	
D.8.4	Route of administration:	
D.8.5	Which IMP is it a placebo for? Specify IMP Number(s) from D.1.1	
D.8.5.1	Composition, apart from the active substance(s):	
D.8.5.2	Is it otherwise identical to the IMP?	**Yes ? No ? Not Answered ?**
D.8.5.2.1	If not, specify major ingredients:	

D.9 SITE(S) WHERE THE QUALIFIED PERSON CERTIFIES BATCH RELEASE[22]

*This section is dedicated to **finished** IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D.1.1 or D.8.2 In the case of multiple sites indicate the product certified by each site*

D.9.1	Do not fill in section D.9.2 for an IMP that: *Has a MA in the EU **and*** *Is sourced from the EU market **and*** *Is used in the trial without modification(e.g. not overencapsulated) **and*** *The packaging and labelling is carried out for local use only as per article 9.2. of the Directive 2005/28/EC (GCP Directive)* If all these conditions are met tick • and list the number(s) of each IMP including placebo from sections D.1.1 and D.8.2 to which this applies **PR1** **PR2** **PR3**

D.9.2	**Who is responsible in the Community for the certification of the finished IMPs?**	
	This site is responsible for certification of (list the number(s) of each IMP including placebo from sections D.1.1 and D.8.2):	**PR1** **PR2** **PR3**

	please tick the appropriate box:	
D.9.2.1	Manufacturer	**Yes •**
D.9.2.2	Importer	**No •**
D.9.2.3	Name of the organisation:	**Manufacturing Unit, Hospital Pharmacy, University Hospital Heidelberg**
D.9.2.4	Address:	
D.9.2.4.1	Street Address	**Im Neuenheimer Feld 670**
D.9.2.4.2	Town/City	**Heidelberg**
D.9.2.4.3	Post Code	**69120**
D.9.2.4.4	Country	**Germany**
D.9.2.5	Give the manufacturing authorisation number:	**DE_BW_01_MIA_2016_0005**
D.9.2.5.1	If No authorisation, give the reasons:	

Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2 of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial at D.9.2 above.

E. GENERAL INFORMATION ON THE TRIAL

This section should be used to provide information about the aims, scope and design of the trial. When the protocol includes a sub-study in the MS concerned section E.2.3 should be completed providing information about the sub-study. To identify it check the sub-study box in the 'Objective of the trial' question below.

E.1	**MEDICAL CONDITION OR DISEASE UNDER INVESTIGATION**
E.1.1	Specify the medical condition(s) to be investigated[23] (free text): **English** **Safety and tolerability in healthy subjects**
E.1.1.1	Medical condition in easily understood language **English** **Safety and tolerability in healthy subjects**
E.1.1.2	Therapeutic area **Not possible to specify**
E.1.2	MedDRA version, system organ class, level, term and classification code[24]: Version System Organ Class Classification Code Term Level
E.1.3	Is any of the conditions being studied a rare disease[25]? **No •**

E.2	**OBJECTIVE OF THE TRIAL**
E.2.1	Main objective: **English** **To assess the safety and tolerability of citrulline and folic acid in combination with vericiguat**
E.2.2	Secondary objectives: **English** **Not applicable**
E.2.3	Is there a sub-study? **No •**
E.2.3.1	If 'Yes', give the full title, date and version of each sub-study and their related objectives:

E.3	**PRINCIPAL INCLUSION CRITERIA *(list the most important)***
	English **•☐Subjects male or female, aged equal 18 years or above** **•☐given written consent to participate in the study.** **•☐Ability to provide written, personally signed, and dated informed consent to participate in the trial, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6, and applicable regulations, prior to any trial-related interventions.**

E.4	**PRINCIPAL EXCLUSION CRITERIA *(list the most important)***
	English **•☐Subject without legal capacity who is unable to understand the nature, scope, significance and consequences of this clinical trial** **•☐Clinically significant or relevant abnormalities in the medical history, physical examination (e.g. heart murmur), ECG and laboratory evaluation as assessed by the investigator,** **•☐Medical disorder that may make the participant unlikely to fully complete the trial, or any condition that presents undue risk from the IMP or trial interventions as judged by the investigator,** **•☐Clinically relevant ongoing or clinically relevant history of physical or psychiatric illness as judged by the investigator,** **•☐Blood pressure < 110/>140 mmHg systolic or < 50/>100 mmHg diastolic, or medical history of orthostatic dysregulation or pathologic response to hemodynamic profile at Screening defined as a difference of >20 mmHg in the systolic pressure between the supine and the standing**

position
•☐History of previous syncope during the last 3 months prior to screening visit
•☐Resting heart rate < 50 bpm or > 90 bpm
•☐QTc prolongation (males > 450ms, females > 460ms)
•☐Atrioventricular block II and III degree
•☐History of bleeding disorders
•☐Acute or chronic illness or clinically relevant finding known or expected to modify absorption, distribution, metabolism, or excretion of vericiguat, citrulline or folate/folic acid,
•☐History of hereditary galactose intolerance, lactase deficiency, or glucose-galactose malabsorption
•☐Clinically relevant findings in any of the following investigations (minor deviations of laboratory values from the normal range can be acceptable, if judged by the investigator to be of no clinical relevance for this trial):
o☐Haemoglobin (Hb) < 12 g/dl (males) or < 11 g/dl (females),
o☐Creatine kinase (CK) not within normal limits (subjects with CK elevations between ULN and ULN x 3 may be included if troponin T is negative)
•☐Subjects with a physical or psychiatric condition which at the investigator's discretion may put the subject at risk, may confound the trial results, or may interfere with the subject's participation in this clinical trial
•☐Known or persistent abuse of medication, drugs or alcohol
Exclusion criteria regarding special restrictions for females:
•☐Current (positive pregnancy test, e.g. ß-HCG test in serum or urine) or planned pregnancy or nursing women
•☐Females of childbearing potential, who are not using and not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilized / hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases
Indication specific exclusion criteria:
•☐Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure, e.g. arginine or riociguat
•☐Creatinine (Crea) clearance (Cl) < 90 ml/min (CKD-EPI-Formel),
•☐Bilirubin > upper limit of normal (ULN) x 1.2; In case of suspected Gilbert's disease: non fasting total bilirubin ≤ ULN x 1.2 and fasting total bilirubin ≤ ULN x 1.5 are acceptable.
•☐Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > ULN x 1.5
•☐Concomitant use of medications/drugs that interact pharmacologically with the investigational drugs (e.g. PDE5 inhibitors, nitrates)
•☐Use of an IMP within 30 d or five times the half-life of the IMP, whichever is longer prior to the expected date of receiving the first dose of IMP or active enrolment in another drug or vaccine clinical trial.
•☐A positive result in a drug screening test,
•☐Intake of medication with impact on platelet function (e.g. NSAIDs) within two weeks prior to the first dose of IMP
•☐Specific contraindications to folate/folic acid: megaloblastic anemia as indication of vitamin B12 deficiency

E.5	**END POINT(S):**	
E.5.1	Primary End Point (repeat as necessary)[26]	
	English	**•☐Laboratory safety data**

●☐**Vital signs**
●☐**Adverse events, especially hypotension, syncope**

E.5.1.1 Timepoint(s) of evaluation of this end point
English **Day 1, Day 7, Day 12, Day 20 (only AEs)**

E.5.2 Secondary End Point (repeat as necessary)
English **Not applicable**

E.5.2.1 Timepoint(s) of evaluation of this end point
English **Not applicable**

E.6	**SCOPE OF THE TRIAL – Tick all boxes where applicable**	
E.6.1	Diagnosis	**No •**
E.6.2	Prophylaxis	**No •**
E.6.3	Therapy	**No •**
E.6.4	Safety	**Yes •**
E.6.5	Efficacy	**No •**
E.6.6	Pharmacokinetic	**No •**
E.6.7	Pharmacodynamic	**No •**
E.6.8	Bioequivalence	**No •**
E.6.9	Dose Response	**No •**
E.6.10	Pharmacogenetic	**No •**
E.6.11	Pharmacogenomic	**No •**
E.6.12	Pharmacoeconomic	**No •**
E.6.13	Others	**No •**
E.6.13.1	If others, specify:	

E.7	**TRIAL TYPE AND PHASE[27]**	
E.7.1	Human pharmacology (Phase I)	**Yes •**
Is it:		
E.7.1.1	First administration to humans	**No •**
E.7.1.2	Bioequivalence study	**No •**
E.7.1.3	Other:	**Yes •**
E.7.1.3.1	If other, please specify:	
	English **Safety and tolerability**	
E.7.2	Therapeutic exploratory (Phase II)	**No •**
E.7.3	Therapeutic confirmatory (Phase III)	**No •**
E.7.4	Therapeutic use(Phase IV)	**No •**

E.8	**DESIGN OF THE TRIAL**	
E.8.1	Controlled	**No •**
	If 'Yes', specify:	
E.8.1.1	Randomised:	**No •**
E.8.1.2	Open:	**Yes •**
E.8.1.3	Single blind:	**No •**
E.8.1.4	Double blind:	**No •**
E.8.1.5	Parallel group:	**No •**
E.8.1.6	Cross over:	**No •**
E.8.1.7	Other:	**No •**
E.8.1.7.1	If other specify:	
E.8.2	If controlled, specify the comparator:	
E.8.2.1	Other medicinal product(s)	**No •**
E.8.2.2	Placebo	**No •**
E.8.2.3	Other	**No •**
E.8.2.3.1	If 'Yes' to other, specify :	

E.8.2.4	Number of treatment arms in the trial	
E.8.3	Single site in the Member State concerned (see also section G):	**Yes •**
E.8.4	Multiple sites in the Member State concerned(see also section G):	**No •**
E.8.4.1	Number of sites anticipated in Member State concerned	
E.8.5	Multiple Member States:	**No •**
E.8.5.1	Number of sites anticipated in the EEA:	
E.8.6	Trial involving sites outside the EEA:	
E.8.6.1	Trial being conducted both within and outside the EEA:	**No •**
E.8.6.2	Trial being conducted completely outside of the EEA:	**No •**
E.8.6.3	If E.8.6.1 or E.8.6.2 are Yes, specify the regions in which trial sites are planned:	
E.8.6.4	If E.8.6.1 or E.8.6.2 are Yes, specify the number of sites anticipated outside of the EEA:	
E.8.7	Trial having an independent data monitoring committee:	**No •**
E.8.8	Definition of the end of trial: If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition: **English** **Last Subject Last Visit**	
E.8.9	Initial estimate of the duration of the trial[28] (years, months and days)	
E.8.9.1	In the Member State concerned	**years months days**
E.8.9.2	In all countries concerned by the trial	**years months days**
E.8.10	Proposed date of start of recruitment	
E.8.10.1	In the Member State concerned	**2022-01-01**
E.8.10.2	In any country	

F. POPULATION OF TRIAL SUBJECTS

F.1	AGE RANGE		
F.1.1	Are the trial subjects under 18? If 'Yes', specify the estimated number of subjects planned in each age range for the whole trial:	Approx. No. of patients[29]	**No •**
F.1.1.1	In utero	()	**No •**
F.1.1.2	Preterm newborn infants (up to gestational age < 37 weeks)	()	**No •**
F.1.1.3	Newborns (0-27 days)	()	**No •**
F.1.1.4	Infants and toddlers (28 days - 23 months)	()	**No •**
F.1.1.5	Children (2-11 years)	()	**No •**
F.1.1.6	Adolescents (12-17 years)	()	**No •**
F.1.2	Adults (18-64 years)	(**8**)	**Yes •**
F.1.3	Elderly (>= 65 years)	()	**No •**

F.2	GENDER	
F.2.1	Female	**Yes •**
F.2.2	Male	**Yes •**

F.3	GROUP OF TRIAL SUBJECTS	
F.3.1	Healthy volunteers	**Yes •**
F.3.2	Patients	**No •**
F.3.3	Specific vulnerable populations	**Yes •**
F.3.3.1	Women of child bearing potential not using contraception	**No •**
F.3.3.2	Women of child bearing potential using contraception	**Yes •**
F.3.3.3	Pregnant women	**No •**
F.3.3.4	Nursing women	**No •**
F.3.3.5	Emergency situation	**No •**
F.3.3.6	Subjects incapable of giving consent personally	**No •**
F.3.3.6.1	If 'Yes', specify:	
F.3.3.7	Others:	**No •**
F.3.3.7.1	If 'Yes', specify:	

F.4	PLANNED NUMBER OF SUBJECTS TO BE INCLUDED:	
F.4.1	In the member state	**8**
F.4.2	For a multinational trial**:**	
F.4.2.1	In the EEA	
F.4.2.2	In the whole clinical trial	

F.5	PLANS FOR TREATMENT OR CARE AFTER THE SUBJECT HAS ENDED HIS/HER PARTICIPATION IN THE TRIAL. **please specify** (free text): **English** **None**

G. CLINICAL TRIAL SITES/INVESTIGATORS IN THE MEMBER STATE CONCERNED BY THIS REQUEST

G.1	CO-ORDINATING INVESTIGATOR (for multicentre trial) and principal investigator (for single centre trial)	
G.1.1	Given name:	**Martin**
G.1.2	Middle name, if applicable:	
G.1.3	Family name:	**Coenen**
G.1.4	Qualification (MD…….)	**MD**
G.1.5	Professional address:	
G.1.5	Institution name	**University Hospital Bonn**
G.1.5	Institution department	**Phase I-Einheit, Studienzentrale (SZB)**
G.1.5.1	Street address	**Venusberg-Campus 1**
G.1.5.2	Town/city	**Bonn**
G.1.5.3	Post code	**53227**
G.1.5.4	Country	**Germany**
G.1.6	Telephone number:	
G.1.7	Fax number:	
G.1.8	E-mail:	**martin.coenen@ukbonn.de**

G.2	PRINCIPAL INVESTIGATORS *(for multicentre trial ; where necessary, use additional forms)*
G.2.1	Given name:
G.2.2	Middle name, if applicable:
G.2.3	Family name:
G.2.4	Qualification (MD…….)
G.2.5	Professional address:
G.2.5	Institution name
G.2.5	Institution department
G.2.5.1	Street address
G.2.5.2	Town/city
G.2.5.3	Post code
G.2.5.4	Country
G.2.6	Telephone number:
G.2.7	Fax number:
G.2.8	E-mail:

G.3	CENTRAL TECHNICAL FACILITIES TO BE USED IN THE CONDUCT OF THE TRIAL **Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised** (repeat as needed for multiple organisations).	
G.3.1	Name of organisation:	**University Hospital Bonn**
G.3.2	Department	**Central Laboratory**
G.3.3	Name of contact person:	
G.3.3.1	Given name	
G.3.3.2	Middle name	
G.3.3.3	Family name	
G.3.4	Address:	
G.3.4.1	Street address	
G.3.4.2	Town/city	
G.3.4.3	Post code	
G.3.4.4	Country	
G.3.5	Telephone number:	
G.3.6	Fax number:	
G.3.7	E-mail:	
G.3.8	Enter the details of any duties subcontracted to this central technical facility in this trial	
G.3.8.1	Routine clinical pathology testing	**No ●**

G.3.8.2	Clinical chemistry	**Yes •**
G.3.8.3	Clinical haematology	**Yes •**
G.3.8.4	Clinical microbiology	**No •**
G.3.8.5	Histopathology	**No •**
G.3.8.6	Serology/ endocrinology	**No •**
G.3.8.7	Analytical chemistry	**No •**
G.3.8.8	ECG analysis/ review	**No •**
G.3.8.9	Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	**No •**
G.3.8.10	Primary/ surrogate endpoint test	**No •**
G.3.8.11	Other Duties subcontracted?	**No •**
G.3.8.11.1	If 'Yes', specify the other duties	

G.4	**NETWORKS TO BE INVOLVED IN THE TRIAL (e.g. Paediatric Networks involved in the trial)**
G.4.1	Name of organisation:
G.4.2	Name of contact person:
G.4.2.1	Given name
G.4.2.2	Middle name
G.4.2.3	Family name
G.4.3	Address:
G.4.3.1	Street address
G.4.3.2	Town/city
G.4.3.3	Post code
G.4.3.4	Country
G.4.4	Telephone number:
G.4.5	Fax number:
G.4.6	E-mail:
G.4.7	Activities carried out by the network:

G.5	**ORGANISATIONS TO WHOM THE SPONSOR HAS TRANSFERRED TRIAL RELATED DUTIES AND FUNCTIONS**	
G.5.1	**Has the sponsor transferred any major or all the sponsor's trial related duties and functions to another organisation or third party?**	**Yes •**

Repeat as necessary for multiple organisations:

G.5.1.1	Organisation name:	**University Hospital Bonn**
G.5.1.2	Organisation department	**Studienzentrale (SZB)**
G.5.1.3	Name of contact person :	
G.5.1.3.1	Given name	
G.5.1.3.2	Middle name	
G.5.1.3.3	Family name	
G.5.1.4	Address:	
G.5.1.4.1	Street address	**Venusberg-Campus 1**
G.5.1.4.2	Town/city	**Bonn**
G.5.1.4.3	Post code	**53227**
G.5.1.4.4	Country	**Germany**
G.5.1.5	Telephone number:	
G.5.1.6	Fax number:	
G.5.1.7	E-mail:	**studienzentrale-szb@ukbonn.de**
G.5.1.8	All tasks of the sponsor	**No •**
G.5.1.9	Monitoring	**No •**
G.5.1.10	Regulatory (e.g. preparation of applications to CA and ethics committee)	**Yes •**
G.5.1.11	Investigator recruitment	**No •**
G.5.1.12	IVRS[30] – treatment randomisation	**No •**
G.5.1.13	Data management	**No •**
G.5.1.14	E-data capture	**No •**

G.5.1.15	SUSAR reporting		**Yes** •
G.5.1.16	Quality assurance auditing		**No** •
G.5.1.17	Statistical analysis		**No** •
G.5.1.18	Medical writing		**No** •
G.5.1.19	Other duties subcontracted?		**Yes** •
G.5.1.19.1	If 'Yes' to other, please specify:	**Project Management**	

H. COMPETENT AUTHORITY / ETHICS COMMITTEE IN THE MEMBER STATE CONCERNED BY THIS REQUEST

H.1	**TYPE OF APPLICATION**	
If this application is addressed to the Competent Authority, please tick the Ethics Committee box and give information on the Ethics committee concerned. If this application is addressed to the Ethics Committee, please tick the Competent Authority box and give the information on the Competent Authority concerned.		
H.1.1	Competent Authority	**No ●**
H.1.2	Ethics Committee	**Yes ●**

H.2	**INFORMATION ON ETHICS COMMITTEE**	
H.2.1	Name:	**Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn**
H.2.2	Address	
H.2.2.1	Street address	**Venusberg-Campus 1**
H.2.2.2	Town/city	**Bonn**
H.2.2.3	Post code	**53227**
H.2.2.4	Country	**Germany**
H.2.3	Date of submission:	**2021-10-04**

H.3	**OPINION**	
H.3.1	To be requested	**No ●**
H.3.2	Pending	**Yes ●**
H.3.3	Given	**No ●**
	If 'Given', specify:	
H.3.3.1	Date of opinion:	
H.3.3.2	Opinion favourable	**No ●**
H.3.3.3	Opinion not favourable	**No ●**
	If not favourable, give:	
H.3.3.3.1	The reasons	
H.3.3.3.2	The eventual anticipated date of resubmission:	

I. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

I.1	I hereby confirm that /confirm on behalf of the sponsor (delete which is not applicable) that: • the information provided is complete; • the attached documents contain an accurate account of the information available; • the clinical trial will be conducted in accordance with the protocol; and • the clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

I.2	**APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY** (as stated in section C.1):
I.2.1	Date:
I.2.2	Signature[31]:
I.2.3	Print name:

I.3	**APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE** (as stated in section C.2):
I.3.1	Date:
I.3.2	Signature[32]:
I.3.3	Print name:

ENDNOTES

[1] Any translation of the protocol should be assigned the same date and version as those in the original document.
[2] International Standard Randomised Controlled Trial Number. Sponsors may wish to use an International Standardised Random Controlled Trial Number (ISRCTN) to identify their trial in addition to the EudraCT number; for instance if their trial is part of a multinational trial with sites outside the Community. They can obtain the number and guidance from the Current Controlled Trials website http://www.controlled-trials.com/isrctn to which there is a link from the EudraCT database website http://eudract.ema.europa.eu. When available they should provide it in Section A.6 of the application form.
[3] US National Clinical Trial (NCT) Numbers required on the FDA clinical trial application form.
[4] For a resubmission following previous withdrawal of an application or unfavourable opinion of an ethics committee, or previous withdrawal of an application or refusal of a request by the competent authority, enter a letter in the sequence, A for first resubmission, B for second, C for third et seq.
[5] In accordance with Article 19 of Directive 2001/20/EC.
[6] The contact point should give functional information rather than details of one "person", in order to avoid the need for update and maintenance of these contact details.
[7] This requires a EudraLink account. (See https://eudract.ema.europa.eu/document.html for details)
[8] According to national legislation.
[9] Available from the Summary of Product Characteristics (SmPC)
[10] According to the Community register on orphan medicinal products (Regulation (EC) n° 141/2000): http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm
[11] Committee for Medicinal Products for Human Use of the European Medicines Agency
[12] To be provided only when there is No trade name. This is the name routinely used by a sponsor to identify the IMP in the CT documentation (protocol, IB…).
[13] To be provided only when there is No trade name. This is a code designated by the sponsor which represents the name routinely used by the sponsor to identify the product in the CT documentation. For example, a code may be used for combinations of drugs or drugs and devices.
[14] Available from the Summary of Product Characteristics (SmPC).
[15] Chemical Abstracts Service.
[16] Complete also section D.4 Cell therapy as defined in Annex 1 part IV of Directive 2001/83/EC as amended.
[17] Complete also section D.5 Gene Therapy as defined in Annex 1 part IV of Directive 2001/83/EC as amended.
[18] Complete also section D.6 - Tissue Engineered Product as defined in Article 2(1)(b) of Regulation1394/2007/EC.
[19] Complete also section D.7
[20] The mode of action should briefly describe the chemical, biochemical, immunological or biological means the IMP uses to effect its pharmaceutical action.
[21] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007 19 July 2007
[22] In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medical Products in the European Union.
[23] In the case of healthy volunteer trials, the intended indication for the product under development should be provided.
[24] Applicants are encouraged to provide the MedDRA lower level term if applicable and classification code. These can be accessed from the EMEA EudraCT website (http://eudract.ema.europa.eu/).
[25] Points to consider on the calculation and reporting of the prevalence of a condition for Orphan drug designation: COM/436/01 (http://www.ema.europa.eu/htms/human/orphans/intro.htm).
[26] The protocol will usually identify a single primary end point but there may be a co-primary end point in some cases and/or a number of secondary end points.
[27] The descriptions of the trial types provided are those recommended in preference to Phases. See page 5 of Community guideline CPMP/ICH/291/95. The development of a new indication after initial approval of a medicine should be considered as a new development plan.
[28] From the first inclusion until the last visit of the last subject.
[29] These numbers will be initial estimates. Applicants will not be required to update this information nor do they constitute an authorisation or restriction on the inclusion of these numbers of patients in the trial. The numbers of subjects whose inclusion is authorised are those set out in the authorised version of the protocol, or subsequent authorised amendments.
[30] Interactive Voice Response System: commonly used for randomisation of treatment and controlling the shipment of stock of product.
[31] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.

[32] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.

Annex 1: Clinical trial Application Form

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

To be filled in by the applicant
The questions in this form for the request for authorisation from the Competent Authority are also relevant for the opinion from an Ethics Committee (it represents module 1 of the form for applying to an ethics committee) and can be used as part of that application. Please indicate the relevant purpose in a box below.

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: **Yes ●**
REQUEST FOR OPINION OF THE ETHICS COMMITTEE: **No ●**

A. TRIAL IDENTIFICATION

A.1	Member State in which the submission is being made:	**Spain - AEMPS**
A.2	EudraCT number:	**2022-003111-28**
A.3	Full title of the trial:	
	English	**Mechanism-based drug REpurPOsing in a subtype of Heart Failure with Preserved Ejection Fraction (REPO-HFPEF)**
	Spanish	**Reposicionamiento farmacológico basado en el mecanismo en un subtipo de insuficiencia cardíaca con fracción de eyección conservada"**
A.3.1	Title of the trial for lay people, in easily understood, i.e. non-technical, language:	
	English	**Study to evaluate safety profile of the combination of vericiguat, L-citrulline and folate in patients with a subtype of heart failure with preserved ejection fraction.**
	Spanish	**Estudio para evaluar el perfil de seguridad de la combinación de vericiguat, L-citrulina y folato en pacientes con un subtipo de insuficiencia cardiaca con fracción de eyección conservada.**
A.3.2	Name or abbreviated title of the trial where available:	
A.4	Sponsor's protocol code number, version and date[1]:	
A.4.1	Sponsor's protocol code number:	**REPO-HFpEF-II**
A.4.2	Sponsor's protocol version:	**3.0**
A.4.3	Sponsor's protocol date:	**2023-03-13**
A.5	Additional international study identifiers (e.g. WHO, ISRCTN[2] , US NCT Number[3]) if available	
A.5.1	ISRCTN number:	
A.5.2	US NCT number:	
A.5.3	WHO Universal Trial Number (UTN):	
A.5.4	Other Identifier:	
A.6	Is this a resubmission?	**No ●**
	If 'Yes', indicate the resubmission letter[4]:	**First Submission**
A.7	Is the trial part of an agreed Paediatric Investigation Plan?	**No ●**
A.8	EMA Decision number of Paediatric Investigation Plan:	

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B.1	**SPONSOR**	
B.1.1	Name of organisation:	**Hospital Clínico Universitario de Valencia**
B.1.2	Name of the person to contact:	
B.1.2.1	Given name	**Julio**
B.1.2.2	Middle name	
B.1.2.3	Family name	**Núñez Villota**
B.1.3	Address:	
B.1.3.1	Street address	**Avda. Menédez Pelayo 4 acc**
B.1.3.2	Town/city	**Valencia**
B.1.3.3	Post code	**46010**
B.1.3.4	Country	**Spain**
B.1.4	Telephone number:	**0034 96 1973536**
B.1.5	Fax number:	**0034 96 1973540**
B.1.6	E-mail:	**gestioncientifica@incliva.es**

B.2	**LEGAL REPRESENTATIVE[5] OF THE SPONSOR IN THE COMMUNITY FOR THE PURPOSE OF THIS TRIAL** (if different from the sponsor)
B.2.1	Name of organisation:
B.2.2	Name of person to contact:
B.2.2.1	Given name
B.2.2.2	Middle name
B.2.2.3	Family name
B.2.3	Address:
B.2.3.1	Street address
B.2.3.2	Town/city
B.2.3.3	Post code
B.2.3.4	Country
B.2.4	Telephone number:
B.2.5	Fax number:
B.2.6	E-mail:

B.3	**STATUS OF THE SPONSOR:**	
B.3.1	Commercial:	**No •**
B.3.2	Non commercial:	**Yes •**

B.4	**Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):**	
B.4.1	Name of organisation:	**University of Maastricht**
B.4.2	Country:	**Netherlands**

B.5	**Contact point[6] designated by the sponsor for further information on the trial**	
B.5.1	Name of organisation:	**Instituto de Investigación Sanitaria INCLIVA**
B.5.2	Functional name of contact point (e.g. "Clinical Trial Information Desk"):	**Sub-Directora Científica**
B.5.3	Address:	
B.5.3.1	Street address	**Avda. Menédez Pelayo 4 acc**
B.5.3.2	Town/city	**Valencia**
B.5.3.3	Post code	**46010**
B.5.3.4	Country	**Spain**
B.5.4	Telephone number:	**0034 96 1973536**
B.5.5	Fax number:	**0034 96 1973540**
B.5.6	E-mail: (use a functional e-mail address rather than a personal one)	**gestioncientifica@incliva.es**

C. APPLICANT IDENTIFICATION, (please tick the appropriate box)

C.1	REQUEST 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	**Yes •**
C.1.4	Complete the details of the applicant below even if they are provided elsewhere on the form:	
C.1.4.1	Name of Organisation:	**Instituto de Investigación Sanitaria INCLIVA**
C.1.4.2	Name of contact person:	
C.1.4.2.1	Given name	**Ana**
C.1.4.2.2	Middle name	
C.1.4.2.3	Family name	**Portolés Monzón**
C.1.4.3	Address:	
C.1.4.3.1	Street address	**Avd. Menendez Pelayo 4 acc**
C.1.4.3.2	Town/city	**Valencia**
C.1.4.3.3	Post code	
C.1.4.3.4	Country	**Spain**
C.1.4.4	Telephone number:	**0034 96 1973536**
C.1.4.5	Fax number:	**0034 96 1973540**
C.1.4.6	E-mail:	**gestioncientifica@incliva.es**
C.1.5	Request to receive a copy of CTA data as XML:	
C.1.5.1	Do you want a copy of the CTA form data saved on EudraCT as an XML file?	**Yes •**
C.1.5.1.1	If Yes provide the e-mail address(es) to which it should be sent (up to 5 addresses): **uicec@incliva.es**	
C.1.5.1.2	Do you want to receive this via password protected link(s)[7]?	**No •**

If you answer No to question C.1.5.1.2 the .xml file will be transmitted by less secure e-mail link(s)

D. INFORMATION ON EACH IMP

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator and each placebo, if applicable. ***For placebo go directly to D.8****. If the trial is performed with several products use extra pages and give each product a sequential number in D.1.1. If the product is a combination product, information should be given for each active substance.*

D.1	**IMP IDENTIFICATION**	
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	**PR1**
D.1.2	IMP being tested	**Yes •**
D.1.3	IMP used as a comparator	**No •**

D.2	**STATUS OF THE IMP**	
D.2.1	Has the IMP to be used in the trial a marketing authorisation?	**Yes •**
If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.		
D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name **Verquvo**	
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	**Bayer AG**
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation?	**No •**
D.2.1.1.4.1	If 'Yes', please specify:	
D.2.1.2	The country that granted the Marketing Authorisation	**Spain**
D.2.1.2.1	Is this the Member State concerned with this application?	**Yes •**

D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active substance?	**No •**
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?	**No •**
D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group[9]	**Yes •**
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other:	**No •**
D.2.2.4.1	If 'Yes', please specify:	

D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD:	**No •**
D.2.3.2	Simplified IMPD:	**No •**
D.2.3.3	Summary of product characteristics (SmPC) only:	**Yes •**
D.2.4	Has the use of the IMP been previously authorised in a	**No •**

	clinical trial conducted by the sponsor in the Community?	
D.2.4.1	If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	**No •**
D.2.5.1	If 'Yes', give the orphan drug designation number[10]**:**	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	**No •**
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP[11]?	**No •**
D.2.6.1.2	National Competent Authority?	**No •**

D.3	**DESCRIPTION OF THE IMP**	
D.3.1	Product name where applicable[12]:	
D.3.2	Product code where applicable[13]:	
D.3.3	ATC codes, if officially registered[14]:	**C01**
D.3.4	Pharmaceutical form (use standard terms):	**Tablet**
D.3.4.1	Is this a specific paediatric formulation?	**No •**
D.3.5	Maximum duration of treatment of a subject according to the protocol: **84 days**	
D.3.6	Dose allowed:	
D.3.6.1	For first trial only:	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	
	Route of administration (relevant to the first dose):	
D.3.6.2	For all trials	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	**752.5 mg milligram(s)**
	Route of administration (relevant to the maximum dose):	**Oral use**
D.3.7	Routes of administration (use standard terms):	**Oral use**

D.3.8	Name of each active substance (INN or proposed INN if available):
D.3.9	Other available name for each active substance (provide all available):
D.3.9.1	CAS[15] number
D.3.9.2	Current sponsor code
D.3.9.3	Other descriptive name
D.3.9.4	EV Substance code
D.3.9.5	Full Molecular formula
D.3.9.6	Chemical/biological description of the Active Substance
D.3.10	Strength (specify all strengths to be used):
D.3.10.1	Concentration unit:
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):
D.3.10.3	Concentration (number).

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	**Yes •**
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP)?	**No •**
Is this a:		
D.3.11.3	Advanced Therapy IMP (ATIMP)?	**No •**
D.3.11.3.1	Somatic cell therapy medicinal product[16]?	**No •**
D.3.11.3.2	Gene therapy medicinal product[17]?	**No •**

D.3.11.3.3	Tissue Engineered Product[18]?	**No** •
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device[19])?	**No** •
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	**No** •
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	**No** •
D.3.11.5	Radiopharmaceutical medicinal product?	**No** •
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	**No** •
D.3.11.7	Plasma derived medicinal product?	**No** •
D.3.11.8	Extractive medicinal product?	**No** •
D.3.11.9	Recombinant medicinal product?	**No** •
D.3.11.10	Medicinal product containing genetically modified organisms?	**No** •
D.3.11.10.1	Has the authorisation for contained use or release been granted?	**No** •
D.3.11.10.2	Is it pending?	**No** •
D.3.11.11	Herbal medicinal product?	**No** •
D.3.11.12	Homeopathic medicinal product?	**No** •
D.3.11.13	Another type of medicinal product?	**No** •
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	
D.3.12	Mode of action (*free text*[20])	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	**No** •
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH?[21]	

D.4	**SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)**	
D.4.1	Origin of cells	
D.4.1.1	Autologous	**No** •
D.4.1.2	Allogeneic	**No** •
D.4.1.3	Xenogeneic	**No** •
D.4.1.3.1	If 'Yes', specify the species of origin:	
D.4.2	Type of cells	
D.4.2.1	Stem cells	**No** •
D.4.2.2	Differentiated cells	**No** •
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes…):	
D.4.2.3	Others:	**No** •
D.4.2.3.1	If others, specify:	

D.5	**GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS**	
D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	**No** •
D.5.3	Ex vivo gene therapy:	**No** •
D.5.4	Type of gene transfer product	
D.5.4.1	Nucleic acid (e.g. plasmid):	**No** •
	If 'Yes', specify if:	
D.5.4.1.1	Naked:	**No** •
D.5.4.1.2	Complexed	**No** •
D.5.4.2	Viral vector:	**No** •
D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, …:	
D.5.4.3	Others	**No** •

D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells:	**No •**
If 'Yes', specify the origin of the cells:		
D.5.5.1	Autologous:	**No •**
D.5.5.2	Allogeneic:	**No •**
D.5.5.3	Xenogeneic:	**No •**
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells…):	

D.6	**TISSUE ENGINEERED PRODUCT**	
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.		
D.6.1	Origin of cells	
D.6.1.1	Autologous	**No •**
D.6.1.2	Allogeneic	**No •**
D.6.1.3	Xenogeneic	**No •**
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	**No •**
D.6.2.2	Differentiated cells	**No •**
D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, …):	
D.6.2.3	Others:	**No •**
D.6.2.3.1	If others, specify:	

D.7	**PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)**	
D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	**No •**
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	**No •**
D.7.4.1.1	Does this medical device have a CE mark?	**No •**
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	**No •**
D.7.4.3	Scaffolds?	**No •**
D.7.4.4	Matrices?	**No •**
D.7.4.5	Other?	**No •**
D.7.4.5.1	If other, specify:	

D.1	**IMP IDENTIFICATION**	
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	**PR2**
D.1.2	IMP being tested	**Yes •**
D.1.3	IMP used as a comparator	**No •**

D.2	**STATUS OF THE IMP**	
D.2.1	Has the IMP to be used in the trial a marketing authorisation?	**Yes •**

If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.

D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name	**Stimol**
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation?	**No •**
D.2.1.1.4.1	If 'Yes', please specify:	
D.2.1.2	The country that granted the Marketing Authorisation	**Spain**
D.2.1.2.1	Is this the Member State concerned with this application?	**Yes •**

D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active substance?	**No •**
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?	**No •**
D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group[9]	**Yes •**
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other:	**No •**
D.2.2.4.1	If 'Yes', please specify:	

D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD:	**No •**
D.2.3.2	Simplified IMPD:	**No •**
D.2.3.3	Summary of product characteristics (SmPC) only:	**Yes •**
D.2.4	Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?	**No •**
D.2.4.1	If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	**No •**
D.2.5.1	If 'Yes', give the orphan drug designation number[10]**:**	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	**No •**
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP[11]?	**No •**
D.2.6.1.2	National Competent Authority?	**No •**

D.3	**DESCRIPTION OF THE IMP**	
D.3.1	Product name where applicable[12]:	
D.3.2	Product code where applicable[13]:	
D.3.3	ATC codes, if officially registered[14]:	**A16AA**
D.3.4	Pharmaceutical form (use standard terms):	**Granules for oral solution**
D.3.4.1	Is this a specific paediatric formulation?	**No •**
D.3.5	Maximum duration of treatment of a subject according to the protocol: **84 days**	

D.3.6	Dose allowed:	
D.3.6.1	For first trial only:	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	
	Route of administration (relevant to the first dose):	
D.3.6.2	For all trials	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	**252 g gram(s)**
	Route of administration (relevant to the maximum dose):	**Oral use**
D.3.7	Routes of administration (use standard terms):	**Oral use**

D.3.8	Name of each active substance (INN or proposed INN if available):
D.3.9	Other available name for each active substance (provide all available):
D.3.9.1	CAS[15] number
D.3.9.2	Current sponsor code
D.3.9.3	Other descriptive name
D.3.9.4	EV Substance code
D.3.9.5	Full Molecular formula
D.3.9.6	Chemical/biological description of the Active Substance
D.3.10	Strength (specify all strengths to be used):
D.3.10.1	Concentration unit:
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):
D.3.10.3	Concentration (number).

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	**Yes •**
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP)?	**No •**
Is this a:		
D.3.11.3	Advanced Therapy IMP (ATIMP)?	**No •**
D.3.11.3.1	Somatic cell therapy medicinal product[16]?	**No •**
D.3.11.3.2	Gene therapy medicinal product[17]?	**No •**
D.3.11.3.3	Tissue Engineered Product[18]?	**No •**
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device[19])?	**No •**
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	**No •**
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	**No •**
D.3.11.5	Radiopharmaceutical medicinal product?	**No •**
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	**No •**
D.3.11.7	Plasma derived medicinal product?	**No •**
D.3.11.8	Extractive medicinal product?	**No •**
D.3.11.9	Recombinant medicinal product?	**No •**
D.3.11.10	Medicinal product containing genetically modified organisms?	**No •**
D.3.11.10.1	Has the authorisation for contained use or release been granted?	**No •**
D.3.11.10.2	Is it pending?	**No •**
D.3.11.11	Herbal medicinal product?	**No •**
D.3.11.12	Homeopathic medicinal product?	**No •**
D.3.11.13	Another type of medicinal product?	**No •**
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	

D.3.12	Mode of action (*free text*[20])	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	**No** •
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH?[21]	

D.4	**SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)**	
D.4.1	Origin of cells	
D.4.1.1	Autologous	**No** •
D.4.1.2	Allogeneic	**No** •
D.4.1.3	Xenogeneic	**No** •
D.4.1.3.1	If 'Yes', specify the species of origin:	
D.4.2	Type of cells	
D.4.2.1	Stem cells	**No** •
D.4.2.2	Differentiated cells	**No** •
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes…):	
D.4.2.3	Others:	**No** •
D.4.2.3.1	If others, specify:	

D.5	**GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS**	
D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	**No** •
D.5.3	Ex vivo gene therapy:	**No** •
D.5.4	Type of gene transfer product	
D.5.4.1	Nucleic acid (e.g. plasmid):	**No** •
	If 'Yes', specify if:	
D.5.4.1.1	Naked:	**No** •
D.5.4.1.2	Complexed	**No** •
D.5.4.2	Viral vector:	**No** •
D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, …:	
D.5.4.3	Others	**No** •
D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells:	**No** •
If 'Yes', specify the origin of the cells:		
D.5.5.1	Autologous:	**No** •
D.5.5.2	Allogeneic:	**No** •
D.5.5.3	Xenogeneic:	**No** •
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells…):	

D.6	**TISSUE ENGINEERED PRODUCT**	
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.		
D.6.1	Origin of cells	
D.6.1.1	Autologous	**No** •
D.6.1.2	Allogeneic	**No** •
D.6.1.3	Xenogeneic	**No** •
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	**No** •
D.6.2.2	Differentiated cells	**No** •

D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, …):	
D.6.2.3	Others:	**No •**
D.6.2.3.1	If others, specify:	

D.7	**PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)**	
D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	**No •**
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	**No •**
D.7.4.1.1	Does this medical device have a CE mark?	**No •**
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	**No •**
D.7.4.3	Scaffolds?	**No •**
D.7.4.4	Matrices?	**No •**
D.7.4.5	Other?	**No •**
D.7.4.5.1	If other, specify:	

D.1	**IMP IDENTIFICATION**	
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	**PR3**
D.1.2	IMP being tested	**Yes •**
D.1.3	IMP used as a comparator	**No •**

D.2	**STATUS OF THE IMP**	
D.2.1	Has the IMP to be used in the trial a marketing authorisation?	**Yes •**
If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.		
D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name **Acfol**	
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation?	**No •**
D.2.1.1.4.1	If 'Yes', please specify:	
D.2.1.2	The country that granted the Marketing Authorisation	**Spain**
D.2.1.2.1	Is this the Member State concerned with this application?	**Yes •**

D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active substance?	**No •**
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?	**No •**

D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group[9]	**Yes •**
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other:	**No •**
D.2.2.4.1	If 'Yes', please specify:	

D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD:	**No •**
D.2.3.2	Simplified IMPD:	**No •**
D.2.3.3	Summary of product characteristics (SmPC) only:	**Yes •**
D.2.4	Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?	**No •**
D.2.4.1	If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	**No •**
D.2.5.1	If 'Yes', give the orphan drug designation number[10]**:**	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	**No •**
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP[11]?	**No •**
D.2.6.1.2	National Competent Authority?	**No •**

D.3	**DESCRIPTION OF THE IMP**	
D.3.1	Product name where applicable[12]:	
D.3.2	Product code where applicable[13]:	
D.3.3	ATC codes, if officially registered[14]:	**B03BB01**
D.3.4	Pharmaceutical form (use standard terms):	**Tablet**
D.3.4.1	Is this a specific paediatric formulation?	**No •**
D.3.5	Maximum duration of treatment of a subject according to the protocol:	
	84 days	
D.3.6	Dose allowed:	
D.3.6.1	For first trial only:	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	
	Route of administration (relevant to the first dose):	
D.3.6.2	For all trials	
	Specify per day or total	**Total •**
	Specify total dose (number and unit):	**420 mg milligram(s)**
	Route of administration (relevant to the maximum dose):	**Oral use**
D.3.7	Routes of administration (use standard terms):	**Oral use**

D.3.8	Name of each active substance (INN or proposed INN if available):
D.3.9	Other available name for each active substance (provide all available):
D.3.9.1	CAS[15] number
D.3.9.2	Current sponsor code
D.3.9.3	Other descriptive name
D.3.9.4	EV Substance code
D.3.9.5	Full Molecular formula
D.3.9.6	Chemical/biological description of the Active Substance
D.3.10	Strength (specify all strengths to be used):
D.3.10.1	Concentration unit:
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):

D.3.10.3	Concentration (number).	

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	**Yes •**
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP)?	**No •**
Is this a:		
D.3.11.3	Advanced Therapy IMP (ATIMP)?	**No •**
D.3.11.3.1	Somatic cell therapy medicinal product[16]?	**No •**
D.3.11.3.2	Gene therapy medicinal product[17]?	**No •**
D.3.11.3.3	Tissue Engineered Product[18]?	**No •**
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device[19])?	**No •**
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	**No •**
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	**No •**
D.3.11.5	Radiopharmaceutical medicinal product?	**No •**
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	**No •**
D.3.11.7	Plasma derived medicinal product?	**No •**
D.3.11.8	Extractive medicinal product?	**No •**
D.3.11.9	Recombinant medicinal product?	**No •**
D.3.11.10	Medicinal product containing genetically modified organisms?	**No •**
D.3.11.10.1	Has the authorisation for contained use or release been granted?	**No •**
D.3.11.10.2	Is it pending?	**No •**
D.3.11.11	Herbal medicinal product?	**No •**
D.3.11.12	Homeopathic medicinal product?	**No •**
D.3.11.13	Another type of medicinal product?	**No •**
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	
D.3.12	Mode of action (*free text*[20])	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	**No •**
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH?[21]	

D.4	**SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)**	
D.4.1	Origin of cells	
D.4.1.1	Autologous	**No •**
D.4.1.2	Allogeneic	**No •**
D.4.1.3	Xenogeneic	**No •**
D.4.1.3.1	If 'Yes', specify the species of origin:	
D.4.2	Type of cells	
D.4.2.1	Stem cells	**No •**
D.4.2.2	Differentiated cells	**No •**
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes…):	
D.4.2.3	Others:	**No •**
D.4.2.3.1	If others, specify:	

D.5	GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS	
D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	**No** •
D.5.3	Ex vivo gene therapy:	**No** •
D.5.4	Type of gene transfer product	
D.5.4.1	Nucleic acid (e.g. plasmid):	**No** •
	If 'Yes', specify if:	
D.5.4.1.1	Naked:	**No** •
D.5.4.1.2	Complexed	**No** •
D.5.4.2	Viral vector:	**No** •
D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, …:	
D.5.4.3	Others	**No** •
D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells:	**No** •
If 'Yes', specify the origin of the cells:		
D.5.5.1	Autologous:	**No** •
D.5.5.2	Allogeneic:	**No** •
D.5.5.3	Xenogeneic:	**No** •
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells…):	

D.6	TISSUE ENGINEERED PRODUCT	
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.		
D.6.1	Origin of cells	
D.6.1.1	Autologous	**No** •
D.6.1.2	Allogeneic	**No** •
D.6.1.3	Xenogeneic	**No** •
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	**No** •
D.6.2.2	Differentiated cells	**No** •
D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, …):	
D.6.2.3	Others:	**No** •
D.6.2.3.1	If others, specify:	

D.7	PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)	
D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	**No** •
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	**No** •
D.7.4.1.1	Does this medical device have a CE mark?	**No** •
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	**No** •
D.7.4.3	Scaffolds?	**No** •
D.7.4.4	Matrices?	**No** •
D.7.4.5	Other?	**No** •
D.7.4.5.1	If other, specify:	

D.8 INFORMATION ON PLACEBO (if relevant; repeat as necessary)

D.8.1	Is there a placebo:	**No •**

D.8.2	This refers to placebo number:	
D.8.3	Pharmaceutical form:	
D.8.4	Route of administration:	
D.8.5	Which IMP is it a placebo for? Specify IMP Number(s) from D.1.1	
D.8.5.1	Composition, apart from the active substance(s):	
D.8.5.2	Is it otherwise identical to the IMP?	**Yes ? No ? Not Answered ?**
D.8.5.2.1	If not, specify major ingredients:	

D.9 SITE(S) WHERE THE QUALIFIED PERSON CERTIFIES BATCH RELEASE[22]

*This section is dedicated to **finished** IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D.1.1 or D.8.2 In the case of multiple sites indicate the product certified by each site*

D.9.1	Do not fill in section D.9.2 for an IMP that: *Has a MA in the EU **and*** *Is sourced from the EU market **and*** *Is used in the trial without modification(e.g. not overencapsulated) **and*** *The packaging and labelling is carried out for local use only as per article 9.2. of the Directive 2005/28/EC (GCP Directive)* If all these conditions are met tick **?**and list the number(s) of each IMP including placebo from sections D.1.1 and D.8.2 to which this applies **PR1** **PR2** **PR3**

D.9.2	**Who is responsible in the Community for the certification of the finished IMPs?** This site is responsible for certification of (list the number(s) of each IMP including placebo from sections D.1.1 and D.8.2): please tick the appropriate box:	
D.9.2.1	Manufacturer	**?**
D.9.2.2	Importer	**?**
D.9.2.3	Name of the organisation:	
D.9.2.4	Address:	
D.9.2.4.1	Street Address	
D.9.2.4.2	Town/City	
D.9.2.4.3	Post Code	
D.9.2.4.4	Country	
D.9.2.5	Give the manufacturing authorisation number:	
D.9.2.5.1	If No authorisation, give the reasons:	

Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2 of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial at D.9.2 above.

E. GENERAL INFORMATION ON THE TRIAL

This section should be used to provide information about the aims, scope and design of the trial. When the protocol includes a sub-study in the MS concerned section E.2.3 should be completed providing information about the sub-study. To identify it check the sub-study box in the 'Objective of the trial' question below.

E.1	**MEDICAL CONDITION OR DISEASE UNDER INVESTIGATION**
E.1.1	Specify the medical condition(s) to be investigated[23] (free text): **English** **Subtype of Heart Failure with Preserved Ejection Fraction** **Spanish** **Subtipo de insuficiencia cardíaca con fracción de eyección preservada**
E.1.1.1	Medical condition in easily understood language **English** **Subtype of Heart Failure** **Spanish** **Subtipo de insuficiencia cardíaca**
E.1.1.2	Therapeutic area **Diseases [C] - Cardiovascular Diseases [C14]**
E.1.2	MedDRA version, system organ class, level, term and classification code[24]:

Version	System Organ Class	Classification Code	Term	Level
20.0	**10007541 - Cardiac disorders**	**10019280**	**Heart failures**	**HLGT**

E.1.3	Is any of the conditions being studied a rare disease[25]?	**No •**

E.2	**OBJECTIVE OF THE TRIAL**
E.2.1	Main objective: **English** **The primary objective of this study is to assess the safety profile of a triple therapy containing Vericiguat, L-Citrulline and Folate in HFpEF patients with optimal medical comorbidity treatment to standard of care** **Spanish** **El objetivo principal de este estudio es evaluar el perfil de seguridad de una terapia triple que contiene Vericiguat, L-Citrulina y folato en pacientes con HFpEF con tratamiento de comorbilidad médica óptimo según la práctica clínica habitual**
E.2.2	Secondary objectives: **English** **Secondary objectives are to investigate possible benefits of treatment on patient reported outcomes and echocardiographic and laboratory findings.** **Spanish** **Los objetivos secundarios son investigar los posibles beneficios del tratamiento sobre los resultados informados por los pacientes y los hallazgos ecocardiográficos y de laboratorio.**
E.2.3	Is there a sub-study? **No •**
E.2.3.1	If 'Yes', give the full title, date and version of each sub-study and their related objectives:

E.3	**PRINCIPAL INCLUSION CRITERIA *(list the most important)***
	English **1. Informed consent obtained before any trial-related activities.** **2. Male or female, age above or equal to 18 years at the time of signing informed consent.** **3. Stable NYHA Class II-III in the last 4-weeks.** **4. LVEF ≥50% by echocardiography during screening.** **5. No hospitalisations due to heart failure between screening and randomisation.** **6. Able to perform the CPET at screening**

	7. KCCQ clinical summary score < 90 at screening. **8. At least one of the following:** **a. Mean pulmonary wedge pressure ≥ 15 mmHg or left ventricular end diastolic pressure (LVEDP) ≥ 15 mmHg documented during catheterisation at rest or pulmonary artery (PA) diastolic pressure measured by implantable monitor ≥ 15 mmHg or pulmonary wedge pressure or LVEDP ≥ 25 mmHg documented during catheterisation at exercise.** **b. NT-proBNP ≥ 220 pg/mL (for patients with sinus rhythm) or NT-proBNP ≥ 660 pg/mL (for patients with persistent/permanent atrial fibrillation); in combination with at least one of the following (documented by echocardiography within 12 months prior to or at screening):** **i. Septal é < 7 cm/sec or lateral é < 10 cm/sec or average E/é ≥ 15** **ii. PA systolic pressure > 35 mmHg** **iii. Left atrial (LA) enlargement (LA width ≥ 3.8 cm or LA length ≥ 5.0 cm or LA area ≥ 20.0 cm2 or LA volume ≥ 55 mL or LA volume index ≥ 29 mL/m2)** **iv. LV hypertrophy with septal thickness or posterior wall thickness ≥ 1.2 cm** **c. Hospitalisation with a primary diagnosis of decompensated heart failure which required intravenous (IV) loop diuretic treatment, within the previous 12 months in combination with at least two of the following (documented by echocardiography within 12 months prior to or at screening):** **i. Septal é < 7 cm/sec or lateral é < 10 cm/sec or average E/é ≥ 15** **ii. PA systolic pressure > 35 mmHg** **iii. LA enlargement (LA width ≥ 3.8 cm or LA length ≥ 5.0 cm or LA area ≥ 20.0 cm2 or LA volume ≥ 55 mL or LA volume index ≥ 29 mL/m2)** **iv. LV hypertrophy with septal thickness or posterior wall thickness ≥ 1.2 cm** **v. Ongoing use of diuretic therapy for at least 30 days prior to screening** **9. Mechanism-based diagnostics inclusion: In patients according to 1-8, plasma levels NOX5 ≥ 105 ng/ml or upregulated apo-sGC levels indicated by an sGCa/sGCs ratio higher than 1.05 (a.u.). NOX5 protein levels are stable enough to be measured in plasma using a NOX5 ELISA for which plasma samples will be diluted 1:200 before measurements. Apo-sGC levels are measured in a blood cell-based assay in which apo-sGC/sGC ratio is demonstrated by the phospho- VASP response induced by an sGC activator and divided by the response induced by an sGC stimulator.**
Spanish	**1. Consentimiento informado obtenido antes de cualquier actividad relacionada con el ensayo.** **2. Hombre o mujer, edad mayor o igual a 18 años al momento de firmar el consentimiento informado.** **3. Clase NYHA II-III estable en las últimas 4 semanas.** **4. FEVI ≥50% por ecocardiografía durante la selección.** **5. Sin hospitalizaciones por insuficiencia cardíaca entre la selección y la aleatorización.** **6. Capacidad para realizar el CPET en la selección** **7. Puntuación del resumen clínico KCCQ < 90 en la selección.** **8. Se cumplen al menos una de las siguientes:** **a. Presión capilar pulmonar ≥ 15mmHg o presión diastólica final del ventrículo izquierdo (LVEDP) ≥ 15mmHg documentada durante el cateterismo en reposo o presión diastólica pulmonar arterial medida por un monitor implantable ≥ 15mmHg o presión capilar pulmonar o LVEPD ≥ 25mmHg documentada durante el cateterismo en el ejercicio.** **b.NT-proBNP ≥ 220 pg/mL (para pacientes con ritmo sinusal) o NT-proBNP ≥ 660 pg/mL (para pacientes con fibrilación auricular persistente/permanente); en combinación con al menos una de las siguientes condiciones (documentado por ecocardiografía en los 12**

meses previos a la selección:
i. Septal é < 7 cm/sec o lateral é < 10 cm/sec o promedio E/é ≥ 15.
ii. Presión sistólica pulmonar arterial > 35 mmHg
iii. Dilatación aurícula izquierda (AI) (ancho AI ≥ 3.8 cm o largo AI ≥ 5.0 cm o área AI ≥ 20.0 cm2 o volumen AI ≥ 55 mL o índice de volumen de AI ≥ 29 mL/m2)
iv. Hipertrofia del ventrículo izquierdo con engrosamiento del septo o de la pared posterior ≥ 1.2 cm.
c. Hospitalización con un diagnóstico primario de descompensación de la insuficiencia cardíaca con requerimientos de tratamiento intravenoso de diuréticos de asa en los 12 meses previos en combinación con al menos dos de las siguientes condiciones (documentado por ecocardiografía en los 12 meses previos a la selección):
i. Septal é < 7 cm/sec o lateral é < 10 cm/sec o promedio E/é ≥ 15.
ii. Presión sistólica pulmonar arterial > 35 mmHg
iii. Dilatación aurícula izquierda (AI) (ancho AI ≥ 3.8 cm o largo AI ≥ 5.0 cm o área AI ≥ 20.0 cm2 o volumen AI ≥ 55 mL o índice de volumen de AI ≥ 29 mL/m2)
iv. Hipertrofia del ventrículo izquierdo con engrosamiento del septo o de la pared posterior ≥ 1.2 cm
v. Uso de terapia diurética en los 30 días previos a la visita de selección.
9. Inclusión de diagnósticos basados en mecanismos: En pacientes según 1-8, niveles plasmáticos de NOX5 ≥ 105 ng/ml o niveles de apo-sGC regulados al alza indicados por una relación sGCa/sGCs superior a 1,05 (a.u.). proteína NOX5 los niveles son lo suficientemente estables para ser medidos en plasma utilizando un ELISA NOX5 para el cual las muestras de plasma se diluirán 1:200 antes de las mediciones. Niveles de Apo-sGC
se miden en un ensayo basado en células sanguíneas en el que la relación apo-sGC/sGC se demuestra mediante el fosfo-Respuesta VASP inducida por un activador de sGC y dividida por la respuesta inducida por un estimulador de sGC.

E.4	**PRINCIPAL EXCLUSION CRITERIA** ***(list the most important)***
English	**1. Has SBP <110 mm Hg or symptomatic hypotension.** **2. Prior history of LVEF<50%** **3. Heart failure decompensation in the last 4 weeks.** **4.Has a known allergy or sensitivity to vericiguat, any of its constituents, or any other sGC stimulator.** **5. Has amyloidosis or sarcoidosis.** **6. Has primary valvular heart disease requiring surgical procedure or intervention or has undergone a vascular surgical procedure or intervention within 3 months before randomization.** **7. Has hypertrophic cardiomyopathy.** **8. Has acute myocarditis or Takotsubo cardiomyopathy.** **9. Has received a heart transplant.** **10. Has tachycardia-induced cardiomyopathy and/or uncontrolled tachyarrhythmia.** **11. Has acute coronary syndrome (unstable angina, NSTEMI, or STEMI), undergone CABG or PCI within 3 months before randomization, or indication for coronary revascularization at the time of randomization.** **12. Has symptomatic carotid stenosis, TIA, or stroke within 3 months before randomization.** **13. Has a history of repaired or unrepaired simple congenital heart disease (eg, atrial or ventricular septal defects, or patent ductus arteriosus) with ongoing hemodynamically significant residual lesions, or any history of complex congenital heart disease (eg, tetralogy of Fallot, transposition of the great arteries, single ventricle disease) regardless of repair status.**

	14. Has active endocarditis or constrictive pericarditis. **15. Has an eGFR based on the CKD-EPI Creatinine Equation of <15 mL/min/1.73 m2 within 30 days before randomization or is on chronic dialysis. For participants with multiple eGFR results during screening, the most recent value will be used to determine eligibility at the Randomization Visit.** **16. Has severe hepatic insufficiency such as with hepatic encephalopathy, hepatic laboratory abnormalities (ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN) or ALBI Grade 3 as defined in Appendix 8 [Fragaki, M., et al 2019]. Screening albumin, ALT, AST, and total bilirubin results within 30 days before randomization may be used for assessment of laboratory abnormalities or the calculation of the ALBI score. For participants with multiple albumin and/or total bilirubin results during screening, the most recent value for each test will be used to calculate ALBI score.** **17. Has malignancy or other noncardiac condition limiting life expectancy to <3 years.** **18. Requires continuous home oxygen for severe pulmonary disease.** **19. Has interstitial lung disease.** **20. Has concurrent or anticipated concomitant use of PDE5 inhibitors such as vardenafil, tadalafil, and sildenafil during the study.** **21. Has concurrent use of an sGC stimulator such as riociguat or vericiguat.** **22. Has participated in another interventional clinical study or has been treated with another investigational product ≤30 days before randomization or plans to participate in any other study or study intervention during this study.** **23. Has a recent history (within the last year) of drug or alcohol abuse or dependence.** **24. Is pregnant or breastfeeding or plans to become pregnant or to breastfeed during the study.** **25. Has a medical disorder, condition, or history thereof that in the opinion of the investigator would impair the participant's ability to participate in or complete the study.** **26. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is an investigational site or Sponsor staff directly involved with this study.**
Spanish	**1. Hipotensión arterial sintomática o TAS < 110 mmHg.** **2. Historial previo de FEVI < 50%** **3. Alergia o sensibilidad conocida al vericiguat o alguno de sus constituyentes o a cualquier otro estimulador de GCs** **5. Amiloidosis o Sarcoidosis** **6. Enfermedad cardiaca valvular primaria que requiera procedimiento quirúrgico o intervención o que haya requerido una intervención quirúrgica vascular o intervención en los 3 meses previos a la aleatorización** **7. Cardiomiopatía hipertrófica** **8. Miocarditis aguda o miocardiopatía de Takotsubo** **9. Trasplante cardiaco previo** **10. Miocardiopatía inducida por taquicardia y/o taquiarritmia no controlada** **11. Síndrome coronario agudo (angina inestable, IMSEST, IAMCEST) que requieran CABG o PCI en los 3 meses previos a la aleatorización o esté indicada la revascularización en el momento de la aleatorización** **12. Estenosis carotídea sintomática, AIT o accidente cerebrovascular en los 3 meses previos a la aleatorización** **13. Historial de cardiopatía congénita reparada o no reparada (ej, defecto septal auricular o ventricular o patent ductus arteriosus) con lesiones residuales hemodinámicamente significativas en curso o historial de cardiopatías complejas (ej, tetralogía de Fallot, transposición de grandes arterias, enfermedad ventrículo único) con independencia del**

estado de reparación.
14. Endocarditis activa o pericarditis constrictiva
15. Niveles de TFG basado en la ecuación de CKD-EPI de < 15mL/min/1.73 m2 en los 30 días previos a la aleatorización o diálisis crónica. Para los participantes con múltiples resultados de TFG durante la selección, se utilizará el valor más reciente para determinar la elegibilidad en la visita de aleatorización.
16. Insuficiencia hepática grave tal como encefalopatía hepática; resultados anormales de laboratorio (ALT o AST ≥3 ULN o bilirrubina total ≥2 ULN) o ALBI grado 3. Los niveles de albúmina, ALT, AST y bilirrubina total obtenidos en los 30 días previos a la aleatorización pueden ser usados para el seguimiento de los resultados anormales de laboratorio o el cálculo del ALBI. Para los participantes con múltiples resultados de albúmina y/o bilirrubina total durante la selección, el valor más reciente de cada prueba será el utilizado para calcular la puntuación de ALBI.
17. Enfermedad maligna u otra condición no cardiaca que limite la esperanza de vida a < de 3 años.
18. Requerimiento continuo de oxígeno en domicilio debido a enfermedad pulmonar grave
19. Enfermedad pulmonar intersticial
20.Uso concomitante o previsión de uso de inhibidores de la PDE5 como vardenafilo, tadalafilo y sildenafilo durante el estudio.
21. Uso concomitante de un estimulador de la GCs como el riociguat o vericiguat
22.Participación en otro estudio clínico intervencional o ha sido tratado con otro producto en investigación en ≤ 30 días previos a la aleatorización o se planifica participación en otro estudio intervencional durante este estudio.
23. Historia reciente (en el año previo) o abuso o dependencia de alcohol o drogas.
24. Embarazada o en período de lactancia o planifica embarazo o lactancia durante el estudio
25. Alteración médica, condición o historial que en opinión del investigador pudiera perjudicar la capacidad del paciente para participar o completar el estudio
26. Ser miembro o tener un familiar directo (ej, esposo(a), familiar/representante legal, hermano (a) o hijos (as)) en el Centro que esté relacionado directamente con el estudio

E.5	**END POINT(S):**	
E.5.1	Primary End Point (repeat as necessary)[26]	
	English	**To evaluate safety profile: All adverse drug reactions (ADR)**
	Spanish	**Evaluar el perfil de seguridad: Todas las reacciones adversas a los medicamentos (RAM)**
E.5.1.1	Timepoint(s) of evaluation of this end point	
	English	**From Baseline (Visit 2) to end of study (Visit 4)**
	Spanish	**Desde la visita basal (visita 2) hasta el final del estudio (Visita 4)**
E.5.2	Secondary End Point (repeat as necessary)	
	English	**All cause mortality over the trial period; change in vital signs over the trial period compared to screening; change in laboratory assessments over the trial course compared to screening; number of heart failure related hospital admission over the trial period**
	Spanish	**Todas las causas de muerte durante el período del estudio; cambios en los signos vitales durante el período del estudio comparado con la**

		selección; cambios en las pruebas de laboratorio durante el estudio comparadas con las selección; número de hospitalizaciones relacionadas con la insuficiencia cardíaca durante el período del estudio
E.5.2.1	Timepoint(s) of evaluation of this end point	
	English	**All visits**
	Spanish	**Todas las visitas**

E.6	**SCOPE OF THE TRIAL – Tick all boxes where applicable**	
E.6.1	Diagnosis	**No •**
E.6.2	Prophylaxis	**No •**
E.6.3	Therapy	**Yes •**
E.6.4	Safety	**Yes •**
E.6.5	Efficacy	**No •**
E.6.6	Pharmacokinetic	**No •**
E.6.7	Pharmacodynamic	**No •**
E.6.8	Bioequivalence	**No •**
E.6.9	Dose Response	**No •**
E.6.10	Pharmacogenetic	**No •**
E.6.11	Pharmacogenomic	**No •**
E.6.12	Pharmacoeconomic	**No •**
E.6.13	Others	**No •**
E.6.13.1	If others, specify:	

E.7	**TRIAL TYPE AND PHASE[27]**	
E.7.1	Human pharmacology (Phase I)	**No •**
Is it:		
E.7.1.1	First administration to humans	**No •**
E.7.1.2	Bioequivalence study	**No •**
E.7.1.3	Other:	**No •**
E.7.1.3.1	If other, please specify:	
E.7.2	Therapeutic exploratory (Phase II)	**Yes •**
E.7.3	Therapeutic confirmatory (Phase III)	**No •**
E.7.4	Therapeutic use(Phase IV)	**No •**

E.8	**DESIGN OF THE TRIAL**		
E.8.1	Controlled	**Yes •**	
	If 'Yes', specify:		
E.8.1.1	Randomised:	**Yes •**	
E.8.1.2	Open:	**Yes •**	
E.8.1.3	Single blind:	**No •**	
E.8.1.4	Double blind:	**No •**	
E.8.1.5	Parallel group:	**Yes •**	
E.8.1.6	Cross over:	**No •**	
E.8.1.7	Other:	**No •**	
E.8.1.7.1	If other specify:		
E.8.2	If controlled, specify the comparator:		
E.8.2.1	Other medicinal product(s)	**Yes •**	
E.8.2.2	Placebo	**No •**	
E.8.2.3	Other	**No •**	
E.8.2.3.1	If 'Yes' to other, specify :		
E.8.2.4	Number of treatment arms in the trial	**2**	
E.8.3	Single site in the Member State concerned (see also section G):		**Yes •**
E.8.4	Multiple sites in the Member State concerned(see also section G):		**No •**
E.8.4.1	Number of sites anticipated in Member State concerned		
E.8.5	Multiple Member States:	**No •**	
E.8.5.1	Number of sites anticipated in the EEA:		

E.8.6	Trial involving sites outside the EEA:	
E.8.6.1	Trial being conducted both within and outside the EEA:	**No •**
E.8.6.2	Trial being conducted completely outside of the EEA:	**No •**
E.8.6.3	If E.8.6.1 or E.8.6.2 are Yes, specify the regions in which trial sites are planned:	
E.8.6.4	If E.8.6.1 or E.8.6.2 are Yes, specify the number of sites anticipated outside of the EEA:	
E.8.7	Trial having an independent data monitoring committee:	**Yes •**
E.8.8	Definition of the end of trial: If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition: **English** **Last visit last subject (LVLS)** **Spanish** **Última visita del último sujeto**	
E.8.9	Initial estimate of the duration of the trial[28] (years, months and days)	
E.8.9.1	In the Member State concerned	**years months days**
E.8.9.2	In all countries concerned by the trial	**years months days**
E.8.10	Proposed date of start of recruitment	
E.8.10.1	In the Member State concerned	
E.8.10.2	In any country	

F. POPULATION OF TRIAL SUBJECTS

F.1	AGE RANGE		
F.1.1	Are the trial subjects under 18? If 'Yes', specify the estimated number of subjects planned in each age range for the whole trial:	Approx. No. of patients[29]	**No •**
F.1.1.1	In utero	()	**No •**
F.1.1.2	Preterm newborn infants (up to gestational age < 37 weeks)	()	**No •**
F.1.1.3	Newborns (0-27 days)	()	**No •**
F.1.1.4	Infants and toddlers (28 days - 23 months)	()	**No •**
F.1.1.5	Children (2-11 years)	()	**No •**
F.1.1.6	Adolescents (12-17 years)	()	**No •**
F.1.2	Adults (18-64 years)	(**21**)	**Yes •**
F.1.3	Elderly (>= 65 years)	(**16**)	**Yes •**

F.2	GENDER	
F.2.1	Female	**Yes •**
F.2.2	Male	**Yes •**

F.3	GROUP OF TRIAL SUBJECTS	
F.3.1	Healthy volunteers	**No •**
F.3.2	Patients	**Yes •**
F.3.3	Specific vulnerable populations	**No •**
F.3.3.1	Women of child bearing potential not using contraception	**No •**
F.3.3.2	Women of child bearing potential using contraception	**No •**
F.3.3.3	Pregnant women	**No •**
F.3.3.4	Nursing women	**No •**
F.3.3.5	Emergency situation	**No •**
F.3.3.6	Subjects incapable of giving consent personally	**No •**
F.3.3.6.1	If 'Yes', specify:	
F.3.3.7	Others:	**No •**
F.3.3.7.1	If 'Yes', specify:	

F.4	PLANNED NUMBER OF SUBJECTS TO BE INCLUDED:	
F.4.1	In the member state	**21**
F.4.2	For a multinational trial**:**	
F.4.2.1	In the EEA	
F.4.2.2	In the whole clinical trial	

F.5 PLANS FOR TREATMENT OR CARE AFTER THE SUBJECT HAS ENDED HIS/HER PARTICIPATION IN THE TRIAL. please specify (free text):

English **At the final visit of the study [Visit 4 (84 ± 10 days)], patients will be asked to return the medication left over from the study, the results of the study will be carefully explained and the doctor will continue with the treatment of the patients following the practice usual clinic of the center. A telephone contact will be made 30 days after the end of the treatment. This call will be made to exclude the possibility of adverse effects after the completion of the study.**

Spanish **En la visita final del estudio [Visita 4 (84 ± 10 días)], se solicitara a los pacientes que devuelvan la medicación sobrante del estudio, se explicaran detenidamente los resultados del estudio y el medico continuará con el tratamiento de los pacientes siguiendo la práctica**

	clínica habitual del centro. Se realizará un contacto telefónico 30 días después del final del tratamiento. Esta llamada se realizará para excluir la posibilidad de efectos adversos después de la finalización del estudio.

G. CLINICAL TRIAL SITES/INVESTIGATORS IN THE MEMBER STATE CONCERNED BY THIS REQUEST

G.1	**CO-ORDINATING INVESTIGATOR (for multicentre trial) and principal investigator (for single centre trial)**	
G.1.1	Given name:	**Julio**
G.1.2	Middle name, if applicable:	
G.1.3	Family name:	**Núñez Villota**
G.1.4	Qualification (MD…….)	
G.1.5	Professional address:	
G.1.5	Institution name	**HOSPITAL CLINICO UNIVERSITARIO DE VALENCIA#Cod. CNH: 460044#**
G.1.5	Institution department	**Servicio de Cardiología**
G.1.5.1	Street address	**AVENIDA BLASCO IBAÑEZ 17**
G.1.5.2	Town/city	**València**
G.1.5.3	Post code	**46010**
G.1.5.4	Country	**Spain**
G.1.6	Telephone number:	
G.1.7	Fax number:	
G.1.8	E-mail:	

G.2	**PRINCIPAL INVESTIGATORS *(for multicentre trial ; where necessary, use additional forms)***
G.2.1	Given name:
G.2.2	Middle name, if applicable:
G.2.3	Family name:
G.2.4	Qualification (MD…….)
G.2.5	Professional address:
G.2.5	Institution name
G.2.5	Institution department
G.2.5.1	Street address
G.2.5.2	Town/city
G.2.5.3	Post code
G.2.5.4	Country
G.2.6	Telephone number:
G.2.7	Fax number:
G.2.8	E-mail:

G.3	**CENTRAL TECHNICAL FACILITIES TO BE USED IN THE CONDUCT OF THE TRIAL** **Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised** (repeat as needed for multiple organisations).
G.3.1	Name of organisation:
G.3.2	Department
G.3.3	Name of contact person:
G.3.3.1	Given name
G.3.3.2	Middle name
G.3.3.3	Family name
G.3.4	Address:
G.3.4.1	Street address
G.3.4.2	Town/city
G.3.4.3	Post code
G.3.4.4	Country
G.3.5	Telephone number:
G.3.6	Fax number:
G.3.7	E-mail:
G.3.8	Enter the details of any duties subcontracted to this central technical facility in this trial

G.3.8.1	Routine clinical pathology testing	**Yes ? No ? Not Answered ?**
G.3.8.2	Clinical chemistry	**Yes ? No ? Not Answered ?**
G.3.8.3	Clinical haematology	**Yes ? No ? Not Answered ?**
G.3.8.4	Clinical microbiology	**Yes ? No ? Not Answered ?**
G.3.8.5	Histopathology	**Yes ? No ? Not Answered ?**
G.3.8.6	Serology/ endocrinology	**Yes ? No ? Not Answered ?**
G.3.8.7	Analytical chemistry	**Yes ? No ? Not Answered ?**
G.3.8.8	ECG analysis/ review	**Yes ? No ? Not Answered ?**
G.3.8.9	Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	**Yes ? No ? Not Answered ?**
G.3.8.10	Primary/ surrogate endpoint test	**Yes ? No ? Not Answered ?**
G.3.8.11	Other Duties subcontracted?	**Yes ? No ? Not Answered ?**
G.3.8.11.1	If 'Yes', specify the other duties	

G.4	**NETWORKS TO BE INVOLVED IN THE TRIAL (e.g. Paediatric Networks involved in the trial)**
G.4.1	Name of organisation:
G.4.2	Name of contact person:
G.4.2.1	Given name
G.4.2.2	Middle name
G.4.2.3	Family name
G.4.3	Address:
G.4.3.1	Street address
G.4.3.2	Town/city
G.4.3.3	Post code
G.4.3.4	Country
G.4.4	Telephone number:
G.4.5	Fax number:
G.4.6	E-mail:
G.4.7	Activities carried out by the network:

G.5	**ORGANISATIONS TO WHOM THE SPONSOR HAS TRANSFERRED TRIAL RELATED DUTIES AND FUNCTIONS**	
G.5.1	**Has the sponsor transferred any major or all the sponsor's trial related duties and functions to another organisation or third party?**	**No •**
Repeat as necessary for multiple organisations:		
G.5.1.1	Organisation name:	
G.5.1.2	Organisation department	
G.5.1.3	Name of contact person :	
G.5.1.3.1	Given name	
G.5.1.3.2	Middle name	
G.5.1.3.3	Family name	
G.5.1.4	Address:	
G.5.1.4.1	Street address	
G.5.1.4.2	Town/city	
G.5.1.4.3	Post code	
G.5.1.4.4	Country	
G.5.1.5	Telephone number:	
G.5.1.6	Fax number:	
G.5.1.7	E-mail:	
G.5.1.8	All tasks of the sponsor	**Yes ? No ? Not Answered ?**
G.5.1.9	Monitoring	**Yes ? No ? Not Answered ?**
G.5.1.10	Regulatory (e.g. preparation of applications to CA and ethics committee)	**Yes ? No ? Not Answered ?**
G.5.1.11	Investigator recruitment	**Yes ? No ? Not Answered ?**
G.5.1.12	IVRS[30] – treatment randomisation	**Yes ? No ? Not Answered ?**
G.5.1.13	Data management	**Yes ? No ? Not Answered ?**
G.5.1.14	E-data capture	**Yes ? No ? Not Answered ?**
G.5.1.15	SUSAR reporting	**Yes ? No ? Not Answered ?**

G.5.1.16	Quality assurance auditing	**Yes ? No ? Not Answered ?**
G.5.1.17	Statistical analysis	**Yes ? No ? Not Answered ?**
G.5.1.18	Medical writing	**Yes ? No ? Not Answered ?**
G.5.1.19	Other duties subcontracted?	**Yes ? No ? Not Answered ?**
G.5.1.19.1	If 'Yes' to other, please specify:	

H. COMPETENT AUTHORITY / ETHICS COMMITTEE IN THE MEMBER STATE CONCERNED BY THIS REQUEST

H.1	**TYPE OF APPLICATION**	
If this application is addressed to the Competent Authority, please tick the Ethics Committee box and give information on the Ethics committee concerned. If this application is addressed to the Ethics Committee, please tick the Competent Authority box and give the information on the Competent Authority concerned.		
H.1.1	Competent Authority	**No ●**
H.1.2	Ethics Committee	**Yes ●**

H.2	**INFORMATION ON ETHICS COMMITTEE**	
H.2.1	Name:	**CEIm del Hospital Clínico Universitario de Valencia**
H.2.2	Address	
H.2.2.1	Street address	**Avda. Vicente Blasco Ibáñez, 17**
H.2.2.2	Town/city	**VALENCIA**
H.2.2.3	Post code	**46010**
H.2.2.4	Country	**Spain**
H.2.3	Date of submission:	

H.3	**OPINION**	
H.3.1	To be requested	**No ●**
H.3.2	Pending	**No ●**
H.3.3	Given	**No ●**
	If 'Given', specify:	
H.3.3.1	Date of opinion:	
H.3.3.2	Opinion favourable	**No ●**
H.3.3.3	Opinion not favourable	**No ●**
	If not favourable, give:	
H.3.3.3.1	The reasons	
H.3.3.3.2	The eventual anticipated date of resubmission:	

I. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

I.1	I hereby confirm that /confirm on behalf of the sponsor (delete which is not applicable) that: • the information provided is complete; • the attached documents contain an accurate account of the information available; • the clinical trial will be conducted in accordance with the protocol; and • the clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

I.2	**APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY** (as stated in section C.1):
I.2.1	Date:
I.2.2	Signature[31]:
I.2.3	Print name:

I.3	**APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE** (as stated in section C.2):
I.3.1	Date:
I.3.2	Signature[32]:
I.3.3	Print name:

ENDNOTES

[1] Any translation of the protocol should be assigned the same date and version as those in the original document.
[2] International Standard Randomised Controlled Trial Number. Sponsors may wish to use an International Standardised Random Controlled Trial Number (ISRCTN) to identify their trial in addition to the EudraCT number; for instance if their trial is part of a multinational trial with sites outside the Community. They can obtain the number and guidance from the Current Controlled Trials website http://www.controlled-trials.com/isrctn to which there is a link from the EudraCT database website http://eudract.ema.europa.eu. When available they should provide it in Section A.6 of the application form.
[3] US National Clinical Trial (NCT) Numbers required on the FDA clinical trial application form.
[4] For a resubmission following previous withdrawal of an application or unfavourable opinion of an ethics committee, or previous withdrawal of an application or refusal of a request by the competent authority, enter a letter in the sequence, A for first resubmission, B for second, C for third et seq.
[5] In accordance with Article 19 of Directive 2001/20/EC.
[6] The contact point should give functional information rather than details of one "person", in order to avoid the need for update and maintenance of these contact details.
[7] This requires a EudraLink account. (See https://eudract.ema.europa.eu/document.html for details)
[8] According to national legislation.
[9] Available from the Summary of Product Characteristics (SmPC)
[10] According to the Community register on orphan medicinal products (Regulation (EC) n° 141/2000): http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm
[11] Committee for Medicinal Products for Human Use of the European Medicines Agency
[12] To be provided only when there is No trade name. This is the name routinely used by a sponsor to identify the IMP in the CT documentation (protocol, IB…).
[13] To be provided only when there is No trade name. This is a code designated by the sponsor which represents the name routinely used by the sponsor to identify the product in the CT documentation. For example, a code may be used for combinations of drugs or drugs and devices.
[14] Available from the Summary of Product Characteristics (SmPC).
[15] Chemical Abstracts Service.
[16] Complete also section D.4 Cell therapy as defined in Annex 1 part IV of Directive 2001/83/EC as amended.
[17] Complete also section D.5 Gene Therapy as defined in Annex 1 part IV of Directive 2001/83/EC as amended.
[18] Complete also section D.6 - Tissue Engineered Product as defined in Article 2(1)(b) of Regulation1394/2007/EC.
[19] Complete also section D.7
[20] The mode of action should briefly describe the chemical, biochemical, immunological or biological means the IMP uses to effect its pharmaceutical action.
[21] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007 19 July 2007
[22] In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medical Products in the European Union.
[23] In the case of healthy volunteer trials, the intended indication for the product under development should be provided.
[24] Applicants are encouraged to provide the MedDRA lower level term if applicable and classification code. These can be accessed from the EMEA EudraCT website (http://eudract.ema.europa.eu/).
[25] Points to consider on the calculation and reporting of the prevalence of a condition for Orphan drug designation: COM/436/01 (http://www.ema.europa.eu/htms/human/orphans/intro.htm).
[26] The protocol will usually identify a single primary end point but there may be a co-primary end point in some cases and/or a number of secondary end points.
[27] The descriptions of the trial types provided are those recommended in preference to Phases. See page 5 of Community guideline CPMP/ICH/291/95. The development of a new indication after initial approval of a medicine should be considered as a new development plan.
[28] From the first inclusion until the last visit of the last subject.
[29] These numbers will be initial estimates. Applicants will not be required to update this information nor do they constitute an authorisation or restriction on the inclusion of these numbers of patients in the trial. The numbers of subjects whose inclusion is authorised are those set out in the authorised version of the protocol, or subsequent authorised amendments.
[30] Interactive Voice Response System: commonly used for randomisation of treatment and controlling the shipment of stock of product.
[31] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.

[32] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.