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

For official use:

Date of receiving the request:	Date of request for additional information:	Grounds for non acceptance / negative opinion :
Date of request for information to make it valid:		Give date:
Date of valid application :	Date of receipt of additional / amended information :	Authorisation / positive opinion:
Date of start of procedure :		Give date:
Competent authority registration number :		Withdrawal of application :
Ethics Committee registration number :		Give date :

A: Trial identification

A1. National Competent Authority:

UK - MHRA

A2. European Clinical Trials Database (EudraCT) number:

2020-002229-27

A3. Full title of the trial:

mulTi-Arm Therapeutic study in pre-ICu patients admitted with Covid-19 – Experimental drugs and mechanisms

A3-1. Title of the trial for lay people, in easily understood, i.e. non-technical, language

mulTi-Arm Therapeutic study in pre-ICu patients admitted with Covid-19 – Experimental drugs and mechanisms (TACTIC-E)

A3-2. Name or abbreviated title of the trial where available:

TACTIC- E (COVID-19)

A4. Sponsor's protocol:

Number: TACTIC-E
Version: 1.0
Date: 27/05/2020

A5-1. ISRCTN number, if available :

A5-2. US NCT number:

NCT04393246

A5-3. Who Universal Trial Reference Number (UTRN)

A5-4. Other Identifiers:

Name	Identifier

A6. Is this a resubmission?

○ Yes ◉ No

A7. Is the trial part of a Paediatric Investigation Plan?

○ Yes ○ No ◉ Not Answered

B: Identification of the sponsor responsible for the request

B1. Sponsor

SP1
Contact person

Name of organisation	Cambridge University Hospitals NHS Foundation Trust
Given name	Stephen
Family name	Kelleher
Address	Research & Development, Box 277, Addenbrooke's Hospital
Town/city	Hills
Post code	CB2 0QQ
Country	UNITED KINGDOM
Telephone	01223348491
Fax	
E-mail	research@addenbrookes.nhs.uk

B2.Legal representative in the European Economic Area for the purpose of this trial
A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal Representative 1

Contact person

Name of organisation

Given name
Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

B3. Status of the sponsor: Non-Commercial

B.4 Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):

Name of organisation	Astrazeneca PLC
Country	UNITED KINGDOM
Name of organisation	Evelo Biosciences Ltd
Country	UNITED KINGDOM

B.5 Contact point designated by the sponsor for further information on the trial:

Name of organisation	Cambridge University Hospitals NHS Foundation Trust
Functional name of contact point	Natalia Igosheva
Street Address	Hills Road
Town/city	Cambridge
Post code	CB2 0QQ
Country	UNITED KINGDOM
Telephone	01223349760
Fax	01223349760
E-mail	ccturegulatory@addenbrookes.nhs.uk

C: Applicant identification

C1. Request for the competent authority

C1-1. Who is responsible for the Clinical Trial Authorisation Application?

Sponsor

C1-4. Complete the details of the applicant below even if they are provided elsewhere on the form:

Contact person

Person or organisation name:	Cambridge University Hospitals NHS Foundation Trust
Contact person Given name	Joseph
Contact person Family name	Cheriyan
Address	Hills Road
Town/city	Cambridge
Post code	CB2 0QQ
Country	UNITED KINGDOM
Telephone	1223274915
Fax	
E-mail	jc403@medschl.cam.ac.uk

C1-5. Do you want a xml file copy of the CTA form data saved on EudraCT?

○ Yes ◉ No ○ Not Answered

C2.Request for ethics commitee

C2-1. Who is responsible for the Clinical Trial Authorisation Application?

.....

C2-5. Complete the details of the applicant below even if they are provided elsewhere on the form

Person or organisation name:	.....
Title:	.....
Forename/Initials:	.....
Surname:	.....
Middlename:	.....
Address:	.....
Town/city:	.....
Post code:	.....
Country:	.....
Telephone:	.....
Fax:	.....
E-mail:	.....

Part D: Investigational Medicinal Products

D: Information on the IMPs

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, if applicable. If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.

Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question D7 using the navigation screen.

D. Investigational medicinal products

PR1 Forxiga 10mg (Dapagliflozin)

PR2 Ambrisentan

PR3 EDP1815

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***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***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Forxiga 10mg (Dapagliflozin)
EV Product Code
Name of the MA holder:
AstraZeneca AB
MA number (if MA granted by a Member State):
EU/1/12/795/007 28 film-coated tablets
Is the IMP modified in relation to its MA?

○ Yes ◉ No ○ Not Answered

Which country granted the MA?
EUROPEAN UNION
Is this the Member State concerned with this application?

○ Yes ◉ No ○ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?

○ Yes ○ No ◉ Not Answered

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?

◯ Yes ◯ No ◉ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group

◯ Yes ◯ No ◉ Not Answered

Other :

◯ Yes ◯ No ◉ Not Answered

D2-3. IMPD submitted:

Full IMPD

◯ Yes ◉ No ◯ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	Forxiga 10mg (Dapagliflozin)
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	A10BK01
D.3.4 Pharmaceutical form (use standard terms)	Film-Coated Tablet
D.3.4.1 Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	14 days

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	○ per day ○ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	

D.3.6.2 Maximum dose allowed	10 mg per day
D.3.6.2 Specify per day or total	◉ per day ○ total ○ Not Answered
D.3.6.2 Specify total dose (number and unit)	140 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Oral Use

D.3.7 Routes of administration for this IMP

Oral Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Dapagliflozin
CAS number:	461432-26-8
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C21H25ClO6

Chemical/biological description of the Active Substance	Dapagliflozin is a highly potent , selective and reversible inhibitor of SGLT2.

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	10

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(•) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (•) No ( ) Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	( ) Yes (•) No ( ) Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	( ) Yes (•) No ( ) Not Answered
Radiopharmaceutical medicinal product?	( ) Yes (•) No ( ) Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	( ) Yes (•) No ( ) Not Answered
Plasma derived medicinal product?	( ) Yes (•) No ( ) Not Answered
Extractive medicinal product?	( ) Yes (•) No ( ) Not Answered
Recombinant medicinal product?	( ) Yes (•) No ( ) Not Answered
Medicinal product containing genetically modified organisms?	( ) Yes (•) No ( ) Not Answered
Herbal medicinal product?	( ) Yes (•) No ( ) Not Answered
Homeopathic medicinal product?	( ) Yes (•) No ( ) Not Answered
Another type of medicinal product?	( ) Yes (•) No ( ) Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

Is it an IMP to be used in a first-in-human clinical trial?	( ) Yes (•) No ( ) Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR2**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***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***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
EV Product Code
Name of the MA holder:
MA number (if MA granted by a Member State):
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?

Is this the Member State concerned with this application?
○ Yes ○ No ◉ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ○ No ○ Not Answered
If 'Yes', give active substance in D.3.8 or D.3.9

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?
◉ Yes ○ No ○ Not Answered
If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered
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.3.1

Other :
○ Yes ◉ No ○ Not Answered

D2-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD
○ Yes ◉ No ○ Not Answered
Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
(●) Yes ( ) No ( ) Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

( ) Yes (●) No ( ) Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

( ) Yes (●) No ( ) Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

( ) Yes (●) No ( ) Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?
( ) Yes (●) No ( ) Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?
( ) Yes (●) No ( ) Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	Ambrisentan
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	C02KX02
D.3.4 Pharmaceutical form (use standard terms)	Film-Coated Tablet
D.3.4.1 Is this a specific paediatric formulation?	( ) Yes (●) No ( ) Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	14 Days

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial

D.3.6.1 Specify per day or total:	◯ per day ◯ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	
D.3.6.2 Maximum dose allowed	5 mg per day
D.3.6.2 Specify per day or total	◉ per day ◯ total ◯ Not Answered
D.3.6.2 Specify total dose (number and unit)	70 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Oral Use

D.3.7 Routes of administration for this IMP

Oral Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	ambrisentan
CAS number:	177036-94-1
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C22H22N2O4
Chemical/biological description of the Active Substance	Ambrisentan is an Endothelin receptor antagonist, and is selective for the type A endothelin receptor.
Strength	
Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	5

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes ◯ No ◯ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◯ Yes ◉ No ◯ Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) (1)	◯ Yes ◉ No ◯ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Ambrisentan is an orally active, propanoic acid-class, ERA selective for the endothelin A (ETA) receptor. Endothelin plays a significant role in the pathophysiology of PAH.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR3**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***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***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

○ Yes ◉ No ○ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ○ No ◉ Not Answered

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?
○ Yes ○ No ◉ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
○ Yes ○ No ◉ Not Answered

Other :
○ Yes ○ No ◉ Not Answered

D2-3. IMPD submitted:

Full IMPD
◉ Yes ○ No ○ Not Answered

Simplified IMPD
○ Yes ◉ No ○ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
○ Yes ◉ No ○ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ◉ No ○ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	EDP1815
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	
D.3.4 Pharmaceutical form (use standard terms)	Capsule
D.3.4.1 Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	14 days

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	◯ per day ◯ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	

D.3.6.2 Maximum dose allowed	1.6 x 10^11 cells (2 capsules) TWICE A DAY (3.2 X 10^11 Cells per day)
D.3.6.2 Specify per day or total	◉ per day ◯ total ◯ Not Answered
D.3.6.2 Specify total dose (number and unit)	
D.3.6.2 Route of administration (relevant to the maximum dose):	

D.3.7 Routes of administration for this IMP

Oral Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	EDP1815
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	EDP1815 is a pharmaceutical preparation of a strain of Prevotella histicola.This is new class of therapeutic agent known as monoclonal microbials.
Strength	
Concentration unit:	
Concentration type:	equal
Concentration number (only use both fields for range):	8.0 x 10^10 cells per capsule

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	○ Yes	◉ No	○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◉ Yes	○ No	○ Not Answered
Is this a:			
Advanced Therapy IMP (ATIMP) (1)	○ Yes	◉ No	○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes	◉ No	○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes	◉ No	○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes	◉ No	○ Not Answered
Plasma derived medicinal product?	○ Yes	◉ No	○ Not Answered
Extractive medicinal product?	○ Yes	◉ No	○ Not Answered
Recombinant medicinal product?	○ Yes	◉ No	○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes	◉ No	○ Not Answered
Herbal medicinal product?	○ Yes	◉ No	○ Not Answered

Homeopathic medicinal product?	◯ Yes ◉ No ◯ Not Answered
Another type of medicinal product?	◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. EDP1815 is an orally administered microbe which exerts systemic anti-inflammatory effects by modifying the activity of immune cells which are resident in the small intestine.it has been shown to increase secretion of antiinflammatory
cytokines, such as interleukin (IL)-10 and IL-27, while inducing minimal production of pro-inflammatory cytokines such as IL-6, tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ), thereby reducing immune activation and inflammation

Is it an IMP to be used in a first-in-human clinical trial?	◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D8. Information on placebo *(if relevant; repeat as necessary)*

D8. Is there a placebo:

◯ Yes ◉ No ◯ Not Answered

D9. Sites responsible for final QP release for distribution to investigators.

D9-1. IMPs and placebos for which no responsible site needs to be identified.

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Finished IMP
PR1

Finished IMP
PR2

Index of Sites where the qualified person certifies batch release

In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medicinal Products in the European Union

D9-2. Who is responsible in the Community for the certification of the finished IMP or placebo?
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 D1 or D7 In the case of multiple sites indicate the product certified by each site.

RS1

Manufacturer

Name of the organisation:	Quay Pharmaceuticals Ltd
Address	Quay House, 28 Parkway Deeside Ind Park
Town/city	Flintshire
Post code	CH5 2NS
Country	UNITED KINGDOM

Give the manufacturing authorisation number
MIA(IMP) Number: MIA(IMP) 20300

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR3

E: Design of the Trial.

E.1 Medical Condition or Disease under Investigation

E1-1. Medical condition or disease under investigation [1]

Specify the medical condition(s) to be investigated (free text) :
SARS-Cov-2

Medical condition in easily understood language
Coronavirus

Identify the therapeutic area
Body processes [G] - Circulatory and Respiratory Physiological Phenomena [G09]

[1] In the case of healthy volunteer trials, the intended indication for the product under development should be provided.

E1-2. MedDRA information [2]

[2] Applicants are encouraged to provide the MedDRA lower level term (LLT) if applicable and classification code.

E1-3. Is any of the conditions being studied a rare disease? [3]

○ Yes ◉ No ○ Not Answered

[3] Refer to "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/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003773.pd

E2. Objective of the trial

E2-1. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To determine if a specific intervention reduces the composite of progression of patients with COVID-19-related disease to organ failure or death.

E2-2. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To identify the pharmacodynamic effects of therapies on biomarkers known to be associated with progression of CRC.

To identify pharmacodynamic effects of the therapies based on their mechanisms of action.

To determine if a specific intervention reduces severity of disease as assessed by the 7-point ordinal scale.

To determine if a specific intervention reduces incidence of the individual endpoints of the composite.

To assess the safety and efficacy of the different arms.

To identify the pharmacodynamic effects of therapies on relevant biomarkers

E2-3. Is there a sub-study?

◯ Yes ◉ No ◯ Not Answered

E3. Please list the principal inclusion criteria (list the most important, max 5000 characters).

To be included in the trial the participant must:
• be aged 18 or over
• have clinical picture strongly suggestive of COVID-19-related disease (with/without positive COVID-19 test) AND
- Risk count (as defined above) >3
OR
- Risk count >=3 if it includes “Radiographic severity score >3”
• be considered an appropriate subject for intervention with immunomodulatory or other disease modifying agents in the opinion of the investigator
• Is able to swallow capsules/tablets

E4. Please list the principal exclusion criteria (list the most important, max 5000 characters).

The presence of any of the following will preclude participant inclusion:

• Inability to supply direct informed consent from patient or from Next of Kin or Independent Healthcare Provider on behalf of patient
• Invasive mechanical ventilation at time of screening
• Contraindications to study drugs, including hypersensitivity to the active substances or any of the excipients
• Currently on any of the study investigational medicinal products
• Concurrent participation in an interventional clinical trial (observational studies allowed)
• Patient moribund at presentation or screening
• Pregnancy at screening
• Unwilling to stop breastfeeding during treatment period
• Known severe hepatic impairment (with or without cirrhosis)
• Stage 4 severe chronic kidney disease or requiring dialysis (i.e. Cockcroft Gault estimated creatinine clearance < 30 ml /min)
• Inability to swallow at screening visit
• Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of a safety concern.
• Patient is taking a systemic immunosuppressive agent such as, but not limited to, oral steroids, methotrexate, azathioprine, ciclosporin or tacrolimus, unless these are given as part of COVID standard of care treatment.
• Type 1 diabetes
• Known idiopathic pulmonary fibrosis
• Previous hospital admission with ketoacidosis
• History of symptomatic heart failure within 3 months of admission
• Sustained blood pressure below 90/60 mmHg at admission
• Metabolic acidosis defined as pH< 7.25 (or venous bicarbonate <15 mmol/l) AND ketones > 3.0 mmol/L
• Alanine transaminase and/or aspartate transaminase (ALT and/or AST) > 3 times the upper limit of normal (only one needs to be measured)

E5-1. What is the primary outcome measure for the study?(max 5000 characters)

Time to incidence (up to Day 14) of any one of the following:

o Death
o Invasive mechanical ventilation
o ECMO
o Cardiovascular organ support (balloon pump or inotropes/ vasopressors)
o Renal failure (Cockcroft-Gault estimated creatinine clearance <15 ml /min), haemofiltration or dialysis

Timepoint(s) of evaluation of this end point (max 800 characters)

Day -1 to Day 14

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.

E5-2. Secondary end point(s) (max 5000 characters)

1. Biomarkers thought to be associated with progression of COVID-19: Ferritin, CRP, D-Dimer, neutrophil to lymphocyte ratio, LDH
2. Change in clinical status as assessed on 7-point ordinal scale compared to baseline
3. Time to each of the individual endpoints of the composite primary outcome measure
4. Proportion of patients with adverse events of special interest in each arm
5. SpO2/FiO2
6. Time to Sp02 >94% on room air (excluding chronically hypoxic individuals)
7. Time to first negative SARS-CoV2 PCR
8. Duration of oxygen therapy (days)
9. Duration of hospitalisation (days)
10. All-cause mortality at day 28
11. Time to clinical improvement (defined as >2 point improvement from day 1 on 7-point ordinal scale)

Timepoint(s) of evaluation of this end point (max 800 characters)
Day -1 to Day 90

E6. What is the scope of the trial?

Diagnosis	○ Yes	○ No	◉ Not Answered
Prophylaxis	◉ Yes	○ No	○ Not Answered
Therapy	○ Yes	○ No	◉ Not Answered
Safety	◉ Yes	○ No	○ Not Answered
Efficacy	◉ Yes	○ No	○ Not Answered
Pharmacokinetic	○ Yes	◉ No	○ Not Answered
Pharmacodynamic	◉ Yes	○ No	○ Not Answered
Bioequivalence	○ Yes	○ No	◉ Not Answered
Dose Response	○ Yes	○ No	◉ Not Answered
Pharmacogenetic	○ Yes	○ No	◉ Not Answered
Pharmacogenomic	○ Yes	○ No	◉ Not Answered
Pharmacoeconomic	○ Yes	○ No	◉ Not Answered
Others	○ Yes	○ No	◉ Not Answered

Specify:

E7-1. Trial type and phase (1)

Human pharmacology (Phase I)	○ Yes	◉ No	○ Not Answered
Therapeutic exploratory (Phase II)	◉ Yes	○ No	○ Not Answered
Therapeutic confirmatory (Phase III)	○ Yes	◉ No	○ Not Answered

Therapeutic use (Phase IV)	○ Yes ◉ No ○ Not Answered

(1) 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.

E8. Design of the Trial.

E8-1. Is the trial design controlled?

◉ Yes ○ No ○ Not Answered

Specify:

Randomised	◉ Yes ○ No ○ Not Answered
Open	◉ Yes ○ No ○ Not Answered
Single blind	○ Yes ◉ No ○ Not Answered
Double blind	○ Yes ◉ No ○ Not Answered
Parallel group	◉ Yes ○ No ○ Not Answered
Cross over	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

E8-2. If controlled, specify the comparator:

Other medicinal product(s)	○ Yes ◉ No ○ Not Answered
Placebo	○ Yes ◉ No ○ Not Answered
Other	◉ Yes ○ No ○ Not Answered

Specify the comparator
Standard of Care
Number of treatment arms in the trial
3

E8-3. Single site in the Member State concerned (see also section G):

○ Yes ◉ No ○ Not Answered

E8-4. Multiple sites in the Member State concerned (see also section G):

◉ Yes ○ No ○ Not Answered

Number of sites anticipated in Member State concerned
14

E8-5. Multiple Member States

○ Yes ◉ No ○ Not Answered

Number of sites anticipated in the Community.

E8-6. Trial being conducted both within and outside the EEA

◯ Yes ◉ No ◯ Not Answered

Trial conducted completely outside EEA

◯ Yes ◉ No ◯ Not Answered

E8-7. Will a data monitoring committee (DMC) be convened?

◯ Yes ◉ No ◯ Not Answered

E8-8.

Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial.
If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition.
The end of trial is 18 months after LPLV.

E8-9. How long do you expect the study to last? (1)

In all countries concerned by the trial
Years: 1 Months: 11 Days: 30

In the MS concerned
Years: 1 Months: 11 Days: 30

(1) *From the first inclusion until the last visit of the last subject.*

E8-10. Recruitment start date

Recruitment start date in MS
01/06/2020
In any country
30/05/2022

(1) *If not provided in the protocol.*

F: Population of Trial Subjects

F1. What is the age span of the trial subjects?

Less than 18 years	○ Yes ◉ No ○ Not Answered	Approx no of participants: 0
Adult (18-64 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 281
Elderly (geater than 65 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 1126

The number of participants 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.

F2. What is the gender of the trial subjects?

Female	◉ Yes ○ No ○ Not Answered
Male	◉ Yes ○ No ○ Not Answered

F3. Please select the categories of the trial subjects:

Healthy volunteers	○ Yes ◉ No ○ Not Answered
Patients	◉ Yes ○ No ○ Not Answered
Specific vulnerable populations	○ Yes ◉ No ○ Not Answered

F4. Planned number of subjects to be included:

In the member state 1407

For a multinational trial:

In the European community: 1407

In the whole clinical trial: 1407

F5. Plans for treatment or care after a subject has ended his/her participation in the trial. ***If it is different from the expected normal treatment, please specify:***

At the end of trial participation, participants will revert back to standard of care as per local policy. Administration of the investigational drug will not be continued outside the trial.

G1. and G2. Investigator Details

G1. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

(●) National coordinating investigator
( ) Principal investigator

Given name	Joseph
Family name	Cheriyan
Qualification (MD...)	MBCHB, MA (Cantab), FRCP
Institution name	Cambridge University Hospitals NHS Foundation Trust
Institution department name	Experimental Medicine & Immuno Therapeutics, ACCI, Level 3, Box 98
Street address	Hills Road
Town/city	Cambridge
Post Code	CB2 0QQ
Country	UNITED KINGDOM
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Fax	
E-mail	jc403@medschl.cam.ac.uk

G2. Other principal Investigators *(for a multicentre trial)*

IN1

Given name	Edward
Family name	Banham-Hall
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IN2

Given name	Helen
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IN3

Given name	Andrew
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IN4

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IN5

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IN6

Given name	Muhammad

Family name	Nisar
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IN7

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IN8

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IN9

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IN10

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IN11

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IN12

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IN13

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IN14

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For multi-centre trials where the CI is also a local PI, please list the CI as a PI at G2 (single-centre).

G3. Central Technical Facility Details

G3. 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.*

Organisation

Central technical facility organisation name	
Central technical facility organisation department	
Contact person Given name	
Contact person Family name	
Street address	
Town/city	
Post code	
Country	
Work Telephone	
Fax	
E-mail	

Enter the details of any duties subcontracted to this central technical facility in this trial:

Routine clinical pathology testing	○ Yes ◉ No ○ Not Answered
Clinical chemistry	○ Yes ◉ No ○ Not Answered
Clinical haematology	○ Yes ◉ No ○ Not Answered
Clinical microbiology	○ Yes ◉ No ○ Not Answered
Histopathology	○ Yes ◉ No ○ Not Answered
Serology / endocrinology	○ Yes ◉ No ○ Not Answered
Analytical chemistry	○ Yes ◉ No ○ Not Answered
ECG analysis / review	○ Yes ◉ No ○ Not Answered
Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	○ Yes ◉ No ○ Not Answered
Primary/ surrogate endpoint test	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

Network organisation details

G4. Network organisation details

Organisation
Contact person Given name
Contact person Middle name
Contact person Family name
Street address
Town/city
PostCode
Country
Telephone number
Fax number
E-mail

Activities carried out by the network

G5. Organisations to whom the sponsor has transferred trial related duties and functions

G5. Subcontractor organisations.
Enter details of central CRO facilities supplying services for at least this Member State.

Organisation
Department

Contact person Given name

Contact person Family name

Street address

Town/city

PostCode

Country

Telephone number

Fax

E-mail

Enter the details of any duties/ functions subcontracted to this sponsor's subcontractor facility in this trial

All tasks of the sponsor:	○ Yes	◉ No	○ Not Answered
Monitoring:	○ Yes	◉ No	○ Not Answered
Regulatory (e.g. preparation of applications to CA and Ethics Committee):	○ Yes	◉ No	○ Not Answered
Investigator recruitment:	○ Yes	◉ No	○ Not Answered
IVRS(1) - treatment randomisation:	○ Yes	◉ No	○ Not Answered
Data management:	○ Yes	◉ No	○ Not Answered
E-data capture:	○ Yes	◉ No	○ Not Answered
SUSAR reporting:	○ Yes	◉ No	○ Not Answered
Quality assurance auditing:	○ Yes	◉ No	○ Not Answered
Statistical analysis:	○ Yes	◉ No	○ Not Answered
Medical writing:	○ Yes	◉ No	○ Not Answered
Other duties subcontracted:	○ Yes	◉ No	○ Not Answered

H: Ethics Committee

H1-1. Type of application
Please tick the Ethics Committee box and give information of the Ethics committee concerned.

Ethics committee ☑

H2-1. Name and address of ethics committee:

Organisation
Work Address

PostCode
Country
Fax

H2-2. Date of submission:

27/05/2020

H2-3. Current status of Ethics Committee Opinion at the time of submission to the National Competent Authority:

○ To be requested ◉ Pending ○ Given

I: Signature Of The Applicant In The Member State

I1. I hereby confirm that /confirm on behalf of the sponsor (tick which is applicable) that:

- [x] The information provided is complete;
- [x] The attached documents contain an accurate account of the information available;
- [x] the clinical trial will be conducted in accordance with the protocol;
- [x] The clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

I2. Applicant of the request for the competent authority (as stated in section C.1):

This section was signed electronically by Dr JOSEPH CHERIYAN on 27/05/2020 17:37.

Job Title/Post:	Consultant Clinical Pharmacologist & Physician
Organisation:	Cambridge University Hospitals NHS Foundation Trust
Email:	jc403@cam.c.uk

J: Checklist

J3. ***For details of the documents required for applications to the MHRA in the UK please see*** ***http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Whattosend/index.htm***