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:

2015-002340-14

A3. Full title of the trial:

Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia

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

REMAP-CAP: Randomised, Embedded, Multi-factorial Adaptive Platform Trial for community acquired pneumonia

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

REMAP-CAP

A4. Sponsor's protocol:

Number:
Version: 3.0
Date: 10/07/2019

A5-1. ISRCTN number, if available :

A5-2. US NCT number:

NCT02735707

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

U1111-1189-1653

A5-4. Other Identifiers:

Name	Identifier
ClinicalTrials.gov	NCT02735707

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	University Medical Centre Utrecht
Given name	Wilma
Family name	van Bentum-Puijk
Address	Heidelberglaan 100 (Room number: Str. 3.116), 3584 CX Utrecht, The Netherlands
Town/city	Utrecht
Post code	3584 CX
Country	NETHERLANDS
Telephone	0887555196
Fax	0887568099
E-mail	W.W.Puijk-2@umcutrecht.nl

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 University Medical Centre Utrecht

Given name	Albert
Family name	Vermaas
Address	Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
Town/city	Utrecht
Post code	3584 CX
Country	NETHERLANDS
Telephone	
Fax	
E-mail	A.M.Vermaas@umcutrecht.nl

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	
Country	

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

Name of organisation	ICNARC
Functional name of contact point	Farah Al-Beidh
Street Address	24 Napier House, High Holborn
Town/city	London
Post code	WC1V 6AZ
Country	UNITED KINGDOM
Telephone	02033110211
Fax	
E-mail	farah.al-beidh@icnarc.org

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:	UMC Utrecht
Contact person Given name	Wilma
Contact person Family name	van Bentum-Puijk
Address	Heidelberglaan 100
Town/city	Utrecht
Post code	3584 CX
Country	NETHERLANDS
Telephone	310887555196
Fax	310887568099
E-mail	w.w.puijk-2@umcutrecht.nl

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 ceftriaxone

PR2 moxifloxacin

PR3 levofloxacin

PR4 piperacilin-tazobactam

PR5 ceftaroline

PR6 amoxicillin-clavulanate

PR7 azithromycin

PR8 clarithromycin

PR10 hydrocortisone

PR11 interferon beta-1a

PR12 anakinra

PR13 Lopinavir/Ritonavir Mylan

PR15 hydroxychloroquine

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:
ceftriaxone
EV Product Code

Name of the MA holder:
RANBAXY (UK)
MA number (if MA granted by a Member State):
PL 14894 / 0342
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	ceftriaxone
D.3.2 Product code where applicable	ceftriaxone
D.3.3 ATC codes, if officially registered	J01DD04
D.3.4 Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
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	1-2g daily of ceftriaxone, once a day infusion for as many days as is clinically necessary

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	ceftriaxone has a well established safety profile in patients with pneumonia. As in normal clinical care patients will be prescribed 1-2mg / day for as long as is clinically necessary
D.3.6.1 Specify per day or total:	◉ per day ◯ total ◯ Not Answered
D.3.6.1 Specify total dose (number and unit)	1-2 g gram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use
D.3.6.2 Maximum dose allowed	4g/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)	4	g gram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use	

D.3.7 Routes of administration for this IMP

Intravascular 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):	ceftriaxone sodium
CAS number:	73384-59-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C18-H18-N8-O7-S3
Chemical/biological description of the Active Substance	
Strength	
Concentration unit:	g gram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	1

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. Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

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:
moxifloxacin
EV Product Code
Name of the MA holder:
Bayer
MA number (if MA granted by a Member State):
PL 00010/0291
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	moxifloxacin
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01MA14
D.3.4 Pharmaceutical form (use standard terms)	Solution For Infusion
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	400mg daily of moxifloxacin, for as many days as is clinically necessary

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	400mg daily of moxifloxacin, for as many days as is clinically necessary
D.3.6.1 Specify per day or total:	(•) per day ( ) total ( ) Not Answered
D.3.6.1 Specify total dose (number and unit)	400 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	400mg
D.3.6.2 Specify per day or total	(•) per day ( ) total ( ) Not Answered
D.3.6.2 Specify total dose (number and unit)	400 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	moxifloxacin hydrochloride
CAS number:	354812-41-2
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C21H24FN3O4
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	1.6

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.* Moxifloxacin inhibits bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) that are required for bacterial DNA replication, transcription and repair	
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

Trade name:
levofloxacin
EV Product Code
Name of the MA holder:
Amneal Pharma Europe Ltd
MA number (if MA granted by a Member State):
PL 42357/0192
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
IRELAND
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

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	levofloxacin
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01MA12
D.3.4 Pharmaceutical form (use standard terms)	Solution For Infusion
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	500 mg once or twice daily for as many days as is clinically necessary (typically 5-10 days)

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	500 mg once or twice daily
D.3.6.1 Specify per day or total:	(●) per day ( ) total ( ) Not Answered
D.3.6.1 Specify total dose (number and unit)	1000 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use
D.3.6.2 Maximum dose allowed	1000 mg /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)	1000 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	levofloxacin hemihydrate
CAS number:	100986-85-4
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C18H20FN3O4
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
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. As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

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: **PR4**
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:
piperacilin-tazobactam
EV Product Code
Name of the MA holder:
Hospira UK Limited
MA number (if MA granted by a Member State):
PL 04515/0374
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	piperacilin-tazobactam
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01C R05
D.3.4 Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
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	4g piperacillin / 0.5g tazobactam given every 6-8 hours Piperacillin/tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes) for as many days as is clinically necessary (typically 5-10 days)

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	Piperacillin/tazobactam 16g / 2g
D.3.6.1 Specify per day or total:	(●) per day ( ) total ( ) Not Answered
D.3.6.1 Specify total dose (number and unit)	16 / 2.0 g gram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	Piperacillin/tazobactam 16 g / 2.0 g
D.3.6.2 Specify per day or total	(●) per day ( ) total ( ) Not Answered
D.3.6.2 Specify total dose (number and unit)	16 / 2.0 g gram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravascular Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	Piperacillin
CAS number:	61477-96-1
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C23H27N5O7S
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	g gram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	4

Active Substance 2

Name of active substance (INN or proposed INN if available):	tazobactam
CAS number:	89786-04-9
Current sponsor code:	

Other descriptive name:

Full Molecular formula C10H12N4O5S

Chemical/biological description of the Active Substance

Strength

Concentration unit: g gram(s)

Concentration type: equal

Concentration number (only use both fields for range): 0.5

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. Piperacillin, a broad spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.
Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases which commonly cause resistance to penicillins and cephalosporins but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum to those bacteria that have acquired resistance to piperacillin

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: **PR5**
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:
ceftaroline
EV Product Code
Name of the MA holder:
Pfizer Ireland Pharmaceuticals
MA number (if MA granted by a Member State):
EU/1/12/785/001
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
IRELAND
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

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	ceftaroline
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01DI02
D.3.4 Pharmaceutical form (use standard terms)	Powder For Concentrate For Solution For Infusion
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	600mg, every 12 hours for as long as is required

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	600mg, every 12 hours
D.3.6.1 Specify per day or total:	(•) per day ( ) total ( ) Not Answered
D.3.6.1 Specify total dose (number and unit)	1200 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	1200mg
D.3.6.2 Specify per day or total	(•) per day ( ) total ( ) Not Answered
D.3.6.2 Specify total dose (number and unit)	1200 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	ceftaroline fosamil acetic acid solvate monohydrate
CAS number:	400827-46-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C24H25N8O10PS4
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	30

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. In vitro studies have shown that ceftaroline is bactericidal and able to inhibit bacterial cell wall synthesis in methicillin-resistant Staphylococcus aureus (MRSA) and penicillin non-susceptible Streptococcus pneumoniae (PNSP) due to its affinity for the altered penicillin-binding proteins (PBPs) found in these organisms

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: **PR6**
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:
amoxicillin-clavulanate
EV Product Code
Name of the MA holder:
Sandoz Ltd
MA number (if MA granted by a Member State):
PL 04416/0634
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	amoxicillin-clavulanate
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01CR02
D.3.4 Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
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	1000 mg/ 200 mg every 6-8 hours for as many days as is clinically necessary (typically 5-10 days)

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	1000 mg/ 200 mg every 6-8 hours
D.3.6.1 Specify per day or total:	◉ per day ○ total ○ Not Answered
D.3.6.1 Specify total dose (number and unit)	4000 / 800 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	total daily dose of 3000 mg amoxicillin and 600 mg clavulanic acid
D.3.6.2 Specify per day or total	◉ per day ○ total ○ Not Answered
D.3.6.2 Specify total dose (number and unit)	4000/800 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	sodium amoxicillin
CAS number:	26787-78-0
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C16H19N3O5S
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	1000

Active Substance 2

Name of active substance (INN or proposed INN if available):	potassium clavulanate
CAS number:	61177-45-5
Current sponsor code:	

Other descriptive name:

Full Molecular formula C8H8NO5.K

Chemical/biological description of the Active Substance

Strength

Concentration unit: mg milligram(s)

Concentration type: equal

Concentration number (only use both fields for range): 200

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. Amoxicillin is a semisynthetic penicillin that inhibits one or more enzymes in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death. Clavulanic acid inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin.

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: **PR7**
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:
azithromycin
EV Product Code
Name of the MA holder:
Aspire Pharma Ltd
MA number (if MA granted by a Member State):
PL 35533/0026
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	azithromycin
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01FA10
D.3.4 Pharmaceutical form (use standard terms)	Powder For Solution For Infusion
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	500 mg administered as a single intravenous daily dose for up to 14 days

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	500 mg administered as a single intravenous daily
D.3.6.1 Specify per day or total:	◯ per day ◯ total ◯ Not Answered
D.3.6.1 Specify total dose (number and unit)	500 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	500 mg administered as a single intravenous daily
D.3.6.2 Specify per day or total	◉ per day ◯ total ◯ Not Answered
D.3.6.2 Specify total dose (number and unit)	500 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	azithromycin dihydrate
CAS number:	83905-01-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C38H72N2O12
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	100

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. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.

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: **PR8**
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:
clarithromycin
EV Product Code
Name of the MA holder:
Mercury Pharmaceuticals Ltd.,
MA number (if MA granted by a Member State):
PL 12762/0404
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	clarithromycin
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J01FA09
D.3.4 Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
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	1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion for upto 14 days

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion.
D.3.6.1 Specify per day or total:	(●) per day ( ) total ( ) Not Answered
D.3.6.1 Specify total dose (number and unit)	1 g gram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion.
D.3.6.2 Specify per day or total	(●) per day ( ) total ( ) Not Answered
D.3.6.2 Specify total dose (number and unit)	1 g gram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	clarithromycin
CAS number:	81103-11-9
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C38H69NO13
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	2

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. The mechanism of action of clarithromycin is based on the inhibition of the protein biosynthesis by its binding to the 50S subunit of the bacterial ribosome.

The 14(R)-hydroxy metabolite of clarithromycin, a product of the metabolisation of the parent substance which is found in humans, also has an antibacterial effect.

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: **PR10**
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:
hydrocortisone
EV Product Code
Name of the MA holder:
Pfizer
MA number (if MA granted by a Member State):
PL 00057/1050
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
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

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	hydrocortisone
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	H02AB09
D.3.4 Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
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	Intravenous Hydrocortisone, 50 milligrams (mg) every 6 hours for up-to 7 days

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	Intravenous Hydrocortisone, 50 milligrams (mg) every 6 hours for up-to 7 days
D.3.6.1 Specify per day or total:	(•) per day ( ) total ( ) Not Answered
D.3.6.1 Specify total dose (number and unit)	200 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Use

D.3.6.2 Maximum dose allowed	200mg
D.3.6.2 Specify per day or total	(•) per day ( ) total ( ) Not Answered
D.3.6.2 Specify total dose (number and unit)	200 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous 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):	hydrocortisone sodium succinate
CAS number:	125-04-2
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C25H34NaO8
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	133.7

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.
Corticosteroids exhibit anti-inflammatory, antipruritic, and vasoconstrictive properties. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system

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: **PR11**
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:
interferon beta-1a
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	interferon beta-1a
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	L03AB07
D.3.4 Pharmaceutical form (use standard terms)	Solution for injection in pre-filled syringe
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	IFN-β1a will be administered once daily for 6 days or until ICU discharge, whichever occurs first.

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)	10 µg microgram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Bolus Use(Noncurrent)

D.3.6.2 Maximum dose allowed	IFN-β1a 10 µg will be diluted in 1 mL of sterile water. The diluted IFN-β1a will be administered as an intravenous bolus injection via a central or peripheral line. The injection will be followed with a 5 mL flush of sterile saline.
D.3.6.2 Specify per day or total	◉ per day ○ total ○ Not Answered
D.3.6.2 Specify total dose (number and unit)	10 µg microgram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Bolus Use(Noncurrent)

D.3.7 Routes of administration for this IMP

Intravenous Bolus Use(Noncurrent)

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):	interferon beta-1a.
CAS number:	145258-61-3
Current sponsor code:	
Other descriptive name:	Rebif
Full Molecular formula	C908H1408N246O252S7
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	µg microgram(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. interferon beta-1a is an immunostimulant. Interferons are a group of endogenous glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties.

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: **PR12**
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:
anakinra
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	anakinra
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	L04AC03
D.3.4 Pharmaceutical form (use standard terms)	Solution for injection/infusion in pre-filled syringe
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	Anakinra will be administered once daily until the patient has been breathing without receiving invasive mechanical ventilation for more than 24 hours or for 14 days in patients who continue to receive invasive mechanical ventilation.

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)	300 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Intravenous Bolus Use(Noncurrent)

D.3.6.2 Maximum dose allowed	300 mg of anakinra will be administered as an intravenous bolus injection via a central or peripheral line once daily. In patients receiving renal replacement therapy, anakinra will be dosed only on alternate days.
D.3.6.2 Specify per day or total	(•) per day ( ) total ( ) Not Answered
D.3.6.2 Specify total dose (number and unit)	300 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Bolus Use(Noncurrent)

D.3.7 Routes of administration for this IMP

Intravenous Bolus Use(Noncurrent)

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):	Anakinra
CAS number:	143090-92-0
Current sponsor code:	
Other descriptive name:	Interleukin-1 receptor antagonist anakinra
Full Molecular formula	C759H1186N208O232S10
Chemical/biological description of the Active Substance	
Strength	
Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	300

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. Anakinra is an immunospressant, it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial 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

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

This refers to the IMP number: **PR13**
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:
Lopinavir/Ritonavir Mylan
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	Lopinavir/Ritonavir Mylan
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	J05AR10
D.3.4 Pharmaceutical form (use standard terms)	
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	Maximum duration of 14 Days. Lopinavir/ritonavir will be administered for a minimum of 5 days, including if discharged from ICU before the end of study day 5.

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)	800/200 mg milligram(s)
D.3.6.1 Route of administration (relevant to the first dose):	Enteral Use

D.3.6.2 Maximum dose allowed	Dosing will be Lopinavir/ritonavir 400/100 mg, administered by the enteral route every 12 hours. The preferred method of administration is two 200/50 mg tablets swallowed whole. In patients with a gastric tube-5ml of 80/20 mg per ml suspension.
D.3.6.2 Specify per day or total	◉ per day ○ total ○ Not Answered
D.3.6.2 Specify total dose (number and unit)	800/200 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Enteral Use

D.3.7 Routes of administration for this IMP

Enteral Use

Gastroenteral 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):	Lopinavir
CAS number:	192725-17-0
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C37H48N4O5
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	400

Active Substance 2

Name of active substance (INN or proposed INN if available):	ritonavir
CAS number:	155213-67-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C37H48N6O5S2
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	100

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. Lopinavir provides the antiviral activity of lopinavir/ritonavir. Lopinavir is an inhibitor of the HIV-1 and
HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the
production of immature, non-infectious virus.

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: **PR15**
Investigational medicinal product category:

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:
hydroxychloroquine
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	hydroxychloroquine
D.3.2 Product code where applicable	
D.3.3 ATC codes, if officially registered	P01B A02
D.3.4 Pharmaceutical form (use standard terms)	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	7 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	1600mg / day -The loading dose will be 800 mg, administered 6-hourly, until 2 doses have been administered. Subsequently, starting 12 hours after the first loading dose, the dose will be 400 mg administered 12-hourly for 12 doses.
D.3.6.2 Specify per day or total	◯ per day ◉ total ◯ Not Answered
D.3.6.2 Specify total dose (number and unit)	6400 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Enteral Use

D.3.7 Routes of administration for this IMP

Oral Use

Enteral 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):	hydroxychloriquine
CAS number:	747-36-4
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C18H26ClN3O
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/g milligram(s)/gram
Concentration type:	equal
Concentration number (only use both fields for range):	200

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.
Hydroxychloroquine is a racemic mixture consisting of an R and S enantiomer. Hydroxychloroquine is an aminoquinoline like chloroquine. It is a commonly prescribed medication in the treatment of uncomplicated malaria and rheumatoid arthritis

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

Finished IMP
PR3

Finished IMP
PR4

Finished IMP
PR5

Finished IMP
PR6

Finished IMP
PR7

Finished IMP
PR8

Finished IMP
PR10

Finished IMP
PR11

Finished IMP
PR12

Finished IMP
PR13

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:

Address

Town/city

Post code

Country

Give the manufacturing authorisation number

If no authorisation, give the reasons:

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

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) :
Community acquired pneumonia, including COVID-19 disease

Medical condition in easily understood language
Community acquired pneumonia, including COVID-19 disease

Identify the therapeutic area

Diseases [C] - Respiratory Tract Diseases [C08]

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

E1-2. MedDRA information (2)

MR1

Version	14.0
Level	LLT
Classification Code	10010120
Term	Community acquired pneumonia

SOC	10021881 - Infections and infestations

(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.*

The primary objective of the REMAP is to identify the effect of a range of interventions to improve outcome of adult patients with severe community acquired pneumonia, who are admitted to ICU. This is defined by all cause mortality at 90 days from the date of enrolment into the trial.

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

The secondary objectives are to determine the effect of the interventions on:
ICU Mortality
ICU length of stay
Hospital length of stay
Ventilator free day censored at 28 days
Organ failure free days censored at 28 days
Survival at 6 months
Health Related quality of life at 6 months including EQ5D5L and WHODAS.
Secondary Antibiotic Domain-specific endpoints(censored at day 90):
1. Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens
2. C. difficile illness based on detection from feces using current standard of care diagnostics used at site
3. Serious adverse event (SAE) as defined in CORE protocol
Secondary Macrolide Domain-specific endpoints (censored at day 90):
1. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.
2. Serious Adverse Events (SAE) as defined in CORE protocol

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).

1. Adult patient admitted to an ICU for severe CAP within 48 hours of hospital admission with:
a) symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain); AND
b)radiological evidence of new onset consolidation (in-patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring organ support with one or more of:
a) Non-invasive or invasive ventilatory support;
b) Receiving infusion of vasopressor or inotropes or both

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

Exclusion criteria
1. Healthcare-associated pneumonia:
a) Prior to this illness, has been an in-patient in any healthcare facility within the last 30 days
b) Resident of a nursing home or long term care facility
2. Death is deemed imminent or inevitable during this hospital admission AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
3. Previous participation in this REMAP within the last 90 days

Patients will be deemed eligible for each treatment domain if they don´t meet any of the following domain specific exclusion criteria

Antibiotic Domain
1. Received more than 48 hours of intravenous antibiotic treatment for this index illness
2. More than 24 hours has elapsed since becoming eligible for this domain
3. Known hypersensitivity to all of the study drugs in the site randomization schedule
4. A specific antibiotic choice is indicated
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Macrolide Duration Domain (if randomised to a beta-lactam plus macrolide intervention within the Antibiotic Domain)
1. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Corticosteroid Domain
1. An indication to prescribe systemic corticosteroids for a reason other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia
2. Have received an immunomodulatory dose of systemic corticosteroid therapy for more than 24 hours prior to the time of enrolment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours.
3. The treating clinician believes that participation in the domain would not be in the best interests of the patient

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

The primary outcome for all domains will be the occurrence of death at 90 days post enrolment.
In patients recruited who are suspected to have COVID-19 disease the primary outcome will be “number of days alive and not admitted to ICU up to day 21

Timepoint(s) of evaluation of this end point (max 800 characters)
The occurrence of death will be collected between day 1 and day 90 from the time of enrolment into the trial until end of the hospital admission.

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. ICU mortality censored at 90 days
2. ICU length of stay censored at 90 days
3. Ventilator free days censored at 28 days
4. Organ failure free days censored at 28 days
5. proportion of intubated patients who receive a tracheostomy censored at 28 days
6. Hospital length of stay censored at 90 days after enrolment
7. Destination at time of hospital discharge
8. Readmission to the index ICU during the index hospitalization in the 90 days following enrolment
9. Survival at 6 months after enrolment
10. HRQol at 6 months after enrolment using the EQ5D
11. Disability status measured at 6 months after enrolment using the WHODAS

Secondary Antibiotic Domain-specific endpoints(censored at day 90):
1. Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens
2. C. difficile illness based on detection from feces using current standard of care diagnostics used at site

3. Serious adverse event (SAE) as defined in CORE protocol
Secondary Macrolide Domain-specific endpoints (censored at day 90):
1. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.
2. Serious Adverse Events (SAE) as defined in CORE protocol

Timepoint(s) of evaluation of this end point (max 800 characters)
90 days or 6 months after enrolment as applicable.

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

Specify the design of the trial
randomised, embedded, multifactorial, adaptive platform trial

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

Number of treatment arms in the trial
24

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
40

E8-5. Multiple Member States

◉ Yes ○ No ○ Not Answered

Number of sites anticipated in the Community.
100

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

◉ Yes ○ No ○ Not Answered

Trial conducted completely outside EEA

○ Yes ◉ No ○ Not Answered

Specify the countries in which trial sites are planned

UNITED KINGDOM

NETHERLANDS

GERMANY

BELGIUM

PORTUGAL

CROATIA

HUNGARY

ROMANIA

AUSTRALIA

NEW ZEALAND

IRELAND

Specify the number of sites anticipated outside of the EEA

20

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 study will end when the required numbers of patients have been recruited, the final follow up visit data for the last patient has collected and the databases have been locked.

The design features of this trial create a 'perpetual' trial whose main objective is to continuously update best patient treatment for the life time of the REMAP, but current EU funding is provided until 2021.

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

In all countries concerned by the trial

Years: 2 Months: 5 Days: 22

In the MS concerned

Years: 3 Months: 1 Days: 31

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

E8-10. Recruitment start date

Recruitment start date in MS

01/06/2018

In any country

10/02/2016

[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: 0
Elderly (geater than 65 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 0

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	
Women of childbearing potential not using contraception	○ Yes ◉ No ○ Not Answered	
Women of child bearing potential using contraception	○ Yes ◉ No ○ Not Answered	
Pregnant women	○ Yes ◉ No ○ Not Answered	
Nursing women	○ Yes ◉ No ○ Not Answered	
Emergency situations	◉ Yes ○ No ○ Not Answered	
Subjects incapable of giving consent personally	◉ Yes ○ No ○ Not Answered	

If yes, please specify:
Patients admitted with community acquired pneumonia will most often need treatment started in a life-threatening
emergency and will be unable to provide informed consent at this time due to reduced mental capacity.

Others	○ Yes ◉ No ○ Not Answered

F4. Planned number of subjects to be included:

In the member state 1200

For a multinational trial:

In the European community: 4000

In the whole clinical trial: 6800

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:***

Not applicable. The interventions will be provided to the patients for the period that they are in the intensive care

unit/hospital.

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	Anthony
Family name	Gordon
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G2. Other principal Investigators *(for a multicentre trial)*

IN2

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IN3

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IN4

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IN5

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IN6

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IN7

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IN8

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IN10

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IN11

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IN14

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IN15

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IN16

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IN18

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IN19

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IN20

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IN21

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IN22

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IN23

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IN24

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IN25

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IN26

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IN27

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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 London - Surrey Borders Research Ethics Committee
Work Address

PostCode
Country
Fax

H2-2. Date of submission:

23/03/2018

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

○ To be requested ○ Pending ◉ Given

If "Given", please specify:
Date of opinion: 18/04/2018
State opinion: ◉ Accepted ○ Not Accepted

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 MSc Wilma Van Bentum-Puijk on 06/04/2020 19:17.

Job Title/Post:	sPM
Organisation:	UMC Utrecht
Email:	w.w.puijk-2@umcutrecht.nl

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***