

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

Site Initiation Visit: <date>; <time>

Site name/ Number: / Nxx

PI: <name>



Evaluating new drugs against COVID-19

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

- ▶ Sponsor: Cambridge University Hospitals NHS Foundation Trust, UK
- ▶ EudraCT Number: 2020-002229-27
- ▶ REC reference: 20/WM/0169
- ▶ IRAS project ID: 283769
- ▶ Funding and drug supply: AstraZeneca and Evelo-Biosciences

- ▶ *2 Investigational Product arms:*
 - ▶ Ambrisentan + Dapagliflozin + std of care;
 - ▶ EDP1815 + std of care
- ▶ *Comparator arm:* Standard of care

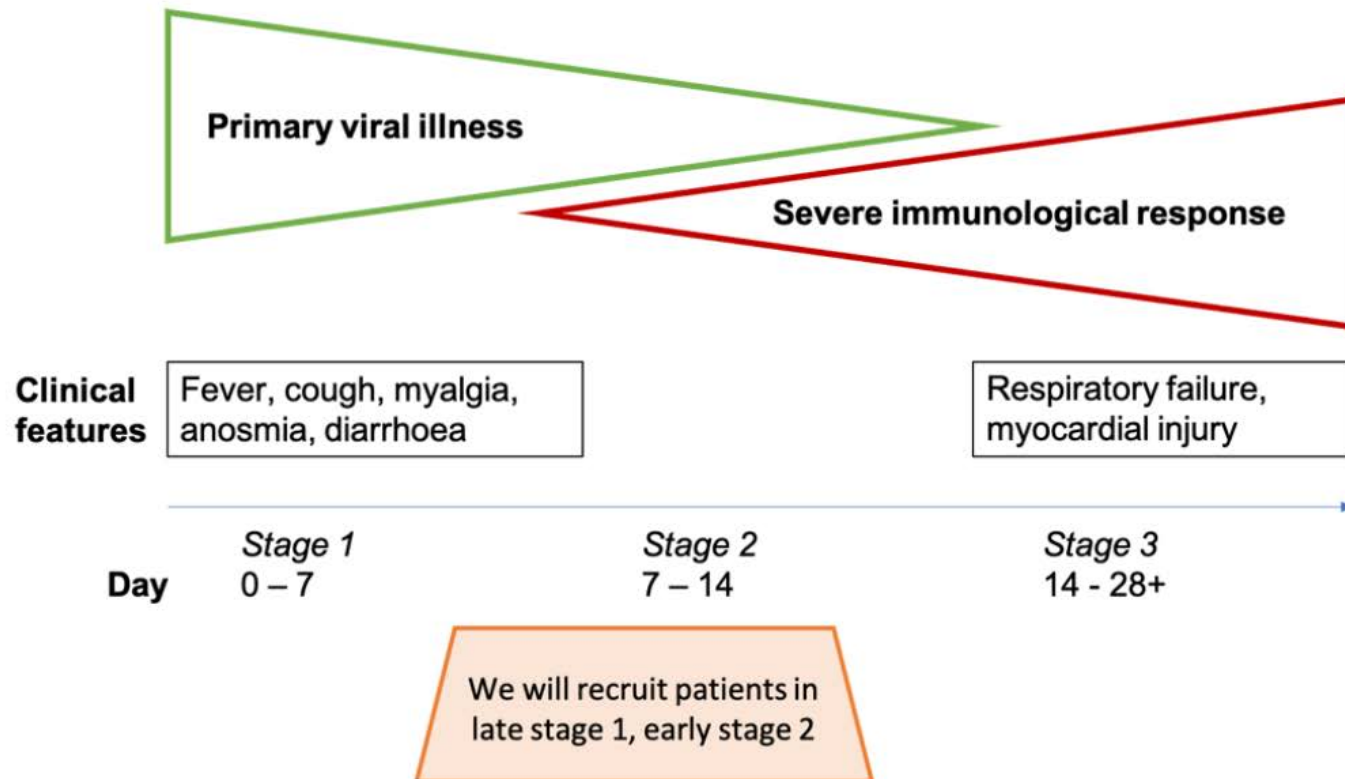


Evaluating new drugs against COVID-19

TACTIC-E

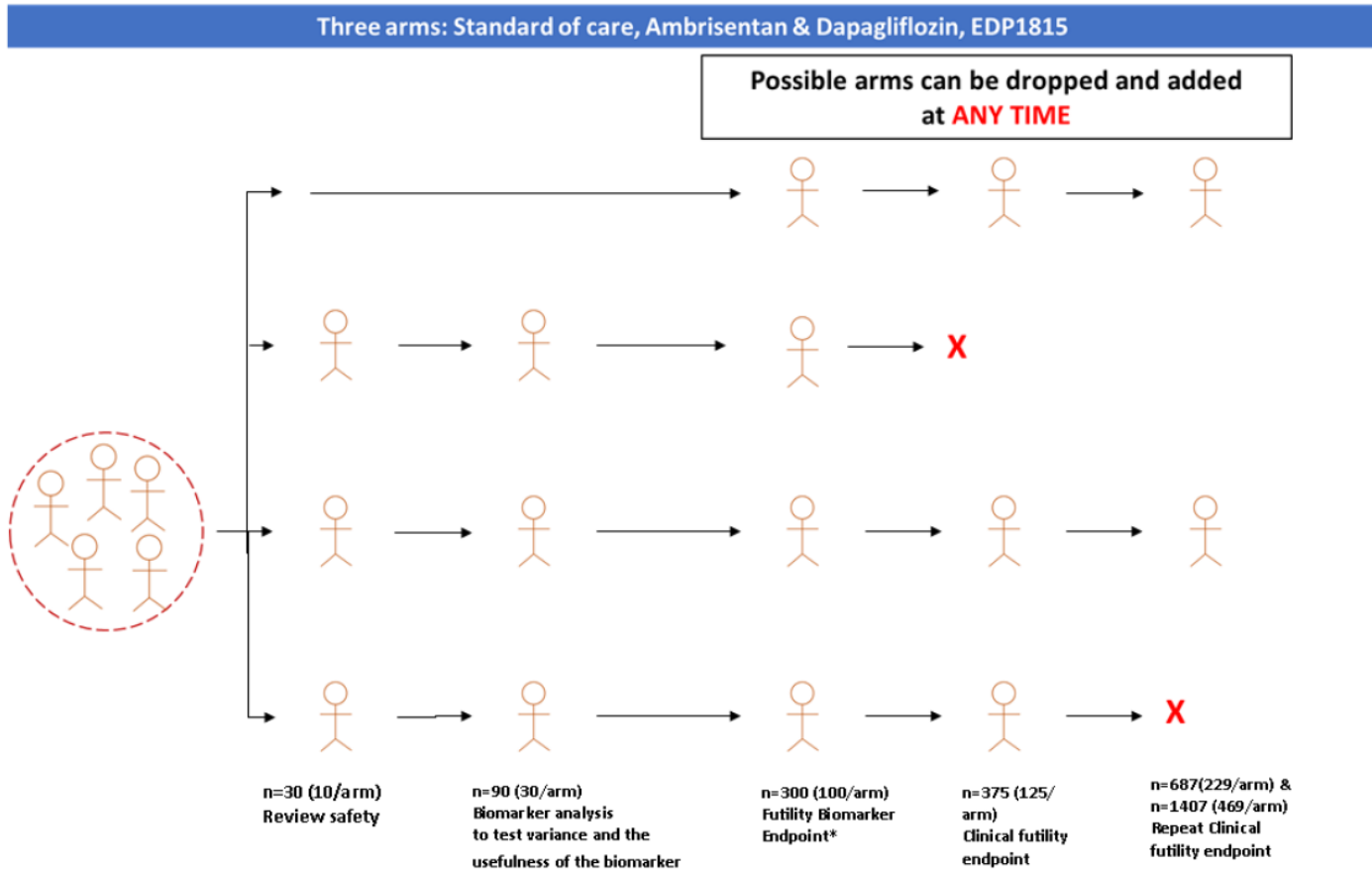
Trial Design and Objectives

Stages of COVID-19-related Disease



Platform design

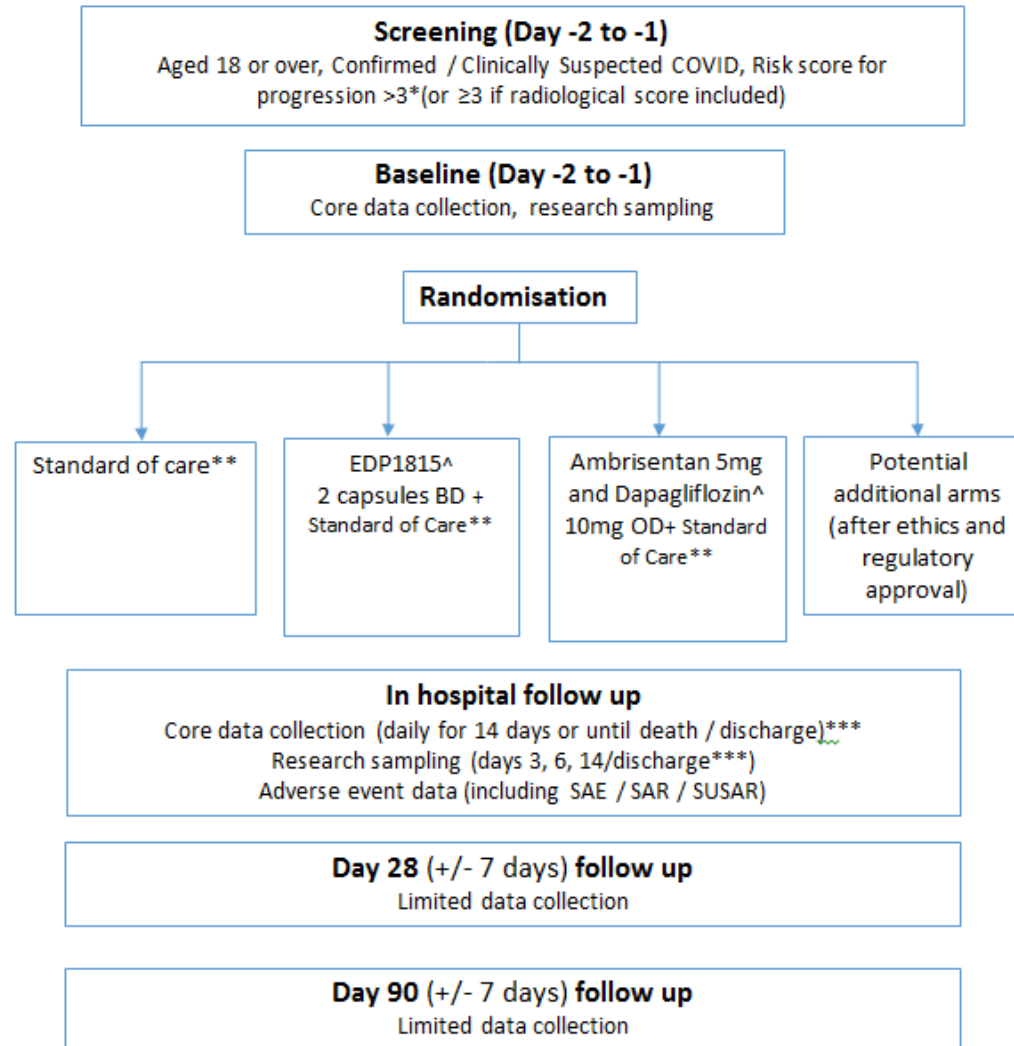
TACTIC-E Trial design



*if a useful biomarker has been identified

WEEKLY MONITORING OF SAFETY PROFILES

Design



TACTIC–E Primary Objective

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

TACTIC-E Secondary objectives

- ▶ To identify the pharmacodynamic effects of therapies biomarkers known to be associated with progression
- ▶ To identify pharmacodynamic effects of the therapies based on their mechanisms of action.
- ▶ To determine if a specific intervention reduces severity of disease as assessed by the 7-point ordinal scale.
- ▶ To determine if a specific intervention reduces incidence of the individual endpoints of the composite.
- ▶ To assess the safety and efficacy of the different arms.
- ▶ To identify the pharmacodynamic effects of therapies on relevant biomarkers

	Pulmonary 7-point scale
1	Death
2	Mechanical invasive ventilation or ECMO
3	Non-invasive ventilation or high flow oxygen
4	Low flow oxygen
5	Hospitalised – no oxygen
6	Discharged; normal activities not resumed
7	Discharged; normal activities resumed

TACTIC-E Exploratory end points

- ▶ To identify clinical or biochemical predictors of response to an intervention
- ▶ Therapy-specific markers of pharmacodynamic response:
 - a. EDP 1815: IL-8, TNF, IL-1 β , IL-10, IL-17, IL-13
 - b. Dapagliflozin and Ambrisentan: serum/plasma ET-1, TNF

Outcome Measures

Primary Outcome Measures

- ▶ Time to incidence (up to Day 14) of any one of the following:
 - ▶ Death
 - ▶ Invasive mechanical ventilation
 - ▶ ECMO (Extracorporeal membrane oxygenation)
 - ▶ Cardiovascular organ support (balloon pump or inotropes/ vasopressors)
 - ▶ Renal failure (Cockcroft–Gault estimated creatinine clearance <15 ml /min), haemofiltration or dialysis

Secondary outcome measures

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

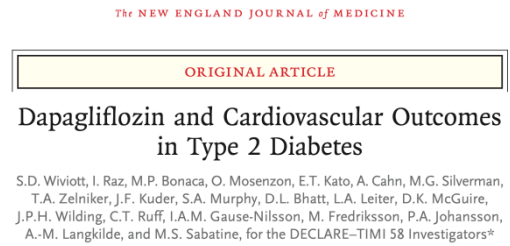
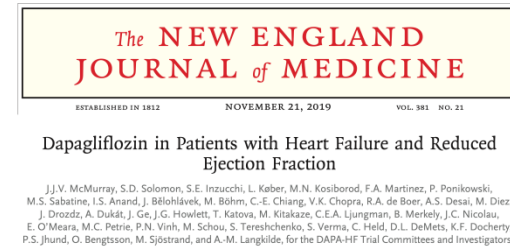


Evaluating new drugs against COVID-19

TACTIC-E IMPs

Dapagliflozin

- ▶ Dapagliflozin is a sodium–glucose co–transporter 2 (SGLT–2) inhibitor
- ▶ Dapagliflozin is licensed for use in the UK for treatment of **Type II diabetes**.
- ▶ **Dose:** 10 mg taken once a day for up to 14 days or discharge, which ever is first. Not for outpatient dosing.
- ▶ Reduces body weight, glucose, HBA1c, blood pressure (within 1–2 weeks), CV events but can cause glycosuria, genital infections, UTI, hypoglycaemia, hypotension. Caution for DKA (Check this **PRIOR** to dosing each day: venous pH < 7.3 or v. bicarb < 15 **AND** blood ketones > 3 mmol/l) – if so stop drug and withdraw subject
- ▶ Shown to reduce risk of worsening HF and mortality in those with Heart Failure with reduced ejection fraction (DAPA–HF trial) irrespective of presence of diabetes
- ▶ DECLARE trial: In T2 Diabetics, dapagliflozin showed no difference to placebo in MACE but did result in lower CV death or hospitalisation for heart failure
- ▶ Well absorbed, Max concn after 2 hours, oral bioavailability 78%, t_{1/2} = 13 hours
- ▶ When used with insulin or insulin secretagogue, consider reduction in insulin/sulphonylurea dose to reduce risk of hypoglycaemia



–McMurray J et al NEJM 2019:1995–2008
–Wiviott SD et al NEJM 2019; 380:347–357
–Saeed MA Drug Des Devel Ther 2014: 8;2493–2505

Ambrisentan

- ▶ Ambrisentan is a selective endothelin receptor A antagonist
- ▶ $t_{1/2}$ 15 hours
- ▶ Ambrisentan was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency and indicated for the treatment of pulmonary arterial hypertension (PAH).
- ▶ **Dose** : 5mg once daily for up to 14 days or discharge, whichever is first. Not for outpatient dosing.
- ▶ **Known teratogenic – do not use in pregnancy and ensure no pregnancy with pregnancy testing till final follow-up where relevant (if necessary at GP practice and retrieve result, if telephone follow-up)**
- ▶ Monitor for LFT dysfunction and anaemia (longer term Rx)
- ▶ It improves exercise capacity, symptoms and haemodynamics in PAH (ARIES1 & ARIES2 trials) with low incidence of LFT abnormalities (in preference of older agents like Bosentan and Sitaxsentan) and AMBITION trial. This was sustained even at 2 years when treated in longterm studies (ARIES-E)

Galie N et al Circulation 2008; 117(23): 3010–9

Galie N et al JACC 2005; 46(3):529–35

Galie N et al NEJM 2015;373(9):834–44

Oudiz RJ et al JACC 2009; 54(21):1971–81

EDP1815

- ▶ EDP1815 is a non-live pharmaceutical preparation of a single strain of *Prevotella histicola* with no genetic modification (monoclonal microbial). Its mechanism of action includes the suppression of excess production of IL-6 and IL-8.
- ▶ EDP1815 is not licensed and is currently in Phase 2 clinical development in Europe and the United States of America.
- ▶ **Dose** is 2 capsules given twice daily (e.g. 1.6×10^{11} cells of EDP1815 in the solid dosage-in-capsule formulation). This will also be given up to 14 days or discharge whichever is first. Not for outpatient dosing.
- ▶ There is no systemic absorption. Needs to be kept refrigerated and used within 24 hours of removal from the fridge.
- ▶ **No Adverse reactions expected – therefore all ARs due to EDP1815 which are serious are SUSARs**



TACTIC-E

Inclusion / Exclusion Criteria

Study Inclusion Criteria

- ▶ To be included in the trial the participant must:
- ▶ be aged 18 or over
- ▶ have clinical picture strongly suggestive of COVID-19–related disease (with/without positive COVID-19 test)

AND

- ▶ – Risk count >3 (described next slide)

OR

- ▶ – Risk count ≥ 3 if it includes “Radiographic severity score >3 ”

- ▶ be considered an appropriate subject for intervention with immunomodulatory or other disease modifying agents in the opinion of the investigator
- ▶ Is able to swallow capsules/tablets

Risk stratification algorithm

Each item scores 1 point

- Radiographic severity score >3
- Male gender
- Non-white ethnicity
- Diabetes
- Hypertension
- Neutrophils $>8.0 \times 10^9/L$
- Age >40 years
- CRP >40 mg/L

Data derived from first 200 patients admitted to King's College Hospital
adapted from Galloway et al, 2020 submitted

Radiographic Severity Score

Score 0–8.

Score each lung separately.

0 = normal

1 = <25% infiltrate

2 = 25–50%

3 = 50–75%

4 = >75%



Radiology, 2019 Mar 27:201160

Radiographic Severity Score

Training available online on TACTIC-E website

https://www.camcovidtrials.net/trials/view,tactice_24.htm

The screenshot shows a web browser window displaying the TACTIC-E website. The browser's address bar shows the URL [camcovidtrials.net/trials/view,tactice_24.htm](https://www.camcovidtrials.net/trials/view,tactice_24.htm). The website header features a green background with a microscopic image of a virus and the text "TACTIC-E". A navigation menu includes "Home", "Patients", "Staff", and "Training & Info". The "Training & Info" section contains a text block stating: "The following video for site staff explains key aspects of the patient recruitment process." Below this is a "Training Materials" dropdown menu with a video titled "TACTIC-R Radiographic Severity Score Practice". At the bottom, the heading "TACTIC-E in numbers" is visible above two empty rectangular boxes.

Study Exclusion Criteria

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

- ▶ Inability to supply direct informed consent from patient or from Next of Kin or Independent Healthcare Provider on behalf of patient
- ▶ Invasive mechanical ventilation at time of screening
- ▶ Contraindications to study drugs, including hypersensitivity to the active substances or any of the excipients
- ▶ Currently on any of the study investigational medicinal products
- ▶ Concurrent participation in an interventional clinical trial (observational studies allowed)
- ▶ Patient moribund at presentation or screening
- ▶ Pregnancy at screening
- ▶ Unwilling to stop breastfeeding during treatment period
- ▶ Known severe hepatic impairment (with or without cirrhosis)
- ▶ Stage 4 severe chronic kidney disease or requiring dialysis (i.e. Cockcroft Gault estimated creatinine clearance < 30 ml /min)
- ▶ Inability to swallow at screening visit
- ▶ Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of a safety concern.

Drug Specific Exclusion Criteria

EDP1815 Specific Exclusions

- ▶ Patient is taking a systemic immunosuppressive agent such as, but not limited to, oral steroids, methotrexate, azathioprine, ciclosporin or tacrolimus, unless these are given as part of COVID standard of care treatment.

Dapagliflozin and Ambrisentan Specific Exclusions

- ▶ Type 1 diabetes
- ▶ Known idiopathic pulmonary fibrosis
- ▶ Previous hospital admission with ketoacidosis
- ▶ History of symptomatic heart failure within 3 months of admission
- ▶ Sustained blood pressure below 90/60 mmHg at admission
- ▶ Metabolic acidosis defined as venous pH < 7.3 (or venous bicarbonate < 15 mmol/l) AND ketones > 3.0 mmol/L)
- ▶ Alanine transaminase and/or aspartate transaminase (ALT and/or AST) > 3 times the upper limit of normal (only one needs to be measured)

Treatment Cessation Criteria – assess daily

- ▶ Alternative clinical diagnosis appears (i.e. no longer considered to have COVID-19-related disease)
- ▶ Patient is discharged from hospital
- ▶ Progression to primary endpoint before dosing with any of the IMPs.
- ▶ Any AE indicating continued treatment is not in the best interest of the subject as assessed by the Investigator
- ▶ Withdrawal of patient consent
- ▶ Unable to take randomised treatment orally
- ▶ Liver dysfunction defined as ALT or AST > 5 ULN (only 1 need be assessed) whilst on study medication for patients randomised to the Ambrisentan and Dapagliflozin treatment arm
- ▶ Metabolic acidosis (venous pH < 7.3 or venous bicarbonate < 15 mmol/l) AND ketones > 3.0 mmol/L at any point during treatment course for patients randomised to the Ambrisentan and Dapagliflozin treatment arm
- ▶ Blood pressure persistently less than 90/60 mmHg in patients randomised to the Ambrisentan and dapagliflozin treatment arm.



Evaluating new drugs against COVID-19

TACTIC-E

Visits / Assessments

Consent

- No trial procedures must be done until patient has consented
- Who takes consent is local PI decision
 - Must be named and delegated on Delegation Log
- Check that consent is taken with current versions of PIS and ICF
- Use ball point pen and initials in boxes where indicated (**not** √ or x)
- Original consent is filed in ISF – 2 copies (1 x patient notes and 1 for patient to take with them)
- Consent dates for patient and consenter MUST match
- Consents to be logged in the TACTIC–E consent tracker

- Consent from patient
- Consent from Legal Representative
 - A legal representative can be asked to give consent on behalf of an adult lacking capacity to do so themselves.
 - They must be given the Legal Representative Information sheet and sign in the assigned space in the main PIS.
 - If a patient who was previously incapacitated regains capacity to consent, this will be sought immediately.

Personal Legal Representative

- ▶ Person NOT connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the patient.
- ▶ Next of Kin
- ▶ Consent from a Next of Kin will be sought as first option if patient is incapable of consenting for themselves

- ▶ Consent from a professional legal representative will be sought if a next of kin is not available in the first instance
- ▶ Doctor responsible for the medical treatment who is independent of the study
- ▶ Person nominated by the healthcare provider

Schedule of Assessments

Data	Screening (Day -2 to Day -1) ^{^ c}	Baseline (Day-2 to Day -1) [^]	D1 [^]	D2	D3 [*]	D4	D5	D6 [*]	D7	D8	D9	D10	D11	D12	D13	Optional D14* or discharge date*	Follow up (~28 days and 90 days)*
Informed consent	x																
Eligibility criteria	x																
Medical history	x																
Physical examination	x																
Vital signs [‡]		x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	
Oxygen therapy status [‡]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Medication review	x				x			x								x	
Clinically indicated blood tests retrieved from medical record: creatinine, ALT or AST ^{‡*}	x ^c				x			x								x	
Routine retrieval and review of relevant clinical data [‡]	x	x			x			x								x	x [*]
Chest X-ray/imaging review for risk score (extracted from medical record, not mandated as part of trial protocol) ^{‡c}	x																x ^c
Pregnancy test (blood/urine)	x																x
Day since onset of symptoms		x			x			x								x	x
Demographics and anthropomorphic data		x															
7-point ordinal scale		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
COVID-19 RTPCR (result may not be available prior to dosing) [‡]		x														x	



Evaluating new drugs against COVID-19

TACTIC-E

Samples / laboratory

TACTIC–E research sample collection

- **Research samples in TACTIC–E are optional – See TPM for details**
- Bloods to be collected (MAX volume 30ml total at each time point):
 - 1x 2.5ml vol RNA Paxgene tube (PAXgene tubes can be taken from stock of TACTIC R, if not then we can provide)
 - 1x EDTA 5ml (for DNA)
 - 1x EDTA 5ml (for plasma)*
 - 1x Serum tube 5ml
- Label tubes with:
 - TACTIC–E
 - Trial ID (e.g. NXX–0001)
 - Collection date (dd/mm/yyyy)
- Time points:
 - Baseline, D3, D6, D14 (or discharge, whichever is sooner, and where feasible), D28**, D90**
 - * TBC whether both DNA and plasma can be processed from same 5ml EDTA tube
 - **–only if visit is conducted face-to-face rather than over the phone

Research sample transfer to labs for processing

- **NOTE:** samples are infectious and should be carefully handled on ward and when transferring to lab.
- Samples processed and stored in a Category 2 lab in the NHS Pathology Lab
- You may need to contact labs **PRIOR** to sampling, to ensure laboratory capacity for processing same-day.
- Blood tubes should be **DOUBLE-BAGGED** and decontaminated prior to leaving ward-wipe outer bag with Clinwipe , or as per your sites Trust policy.



Evaluating new drugs against COVID-19

TACTIC-E

Randomisation

Unique Trial ID number

- ▶ The patient will be assigned a trial ID formatted as
- ▶ Nxx-xxxx where Nxx is the site specific ID and xxxx is the patient number at that specific site
- ▶ ID number will increase sequentially
- ▶ E.g. for your site:
 - <site name>: Nxx-0001, Nxx-0002, Nxx-0003...

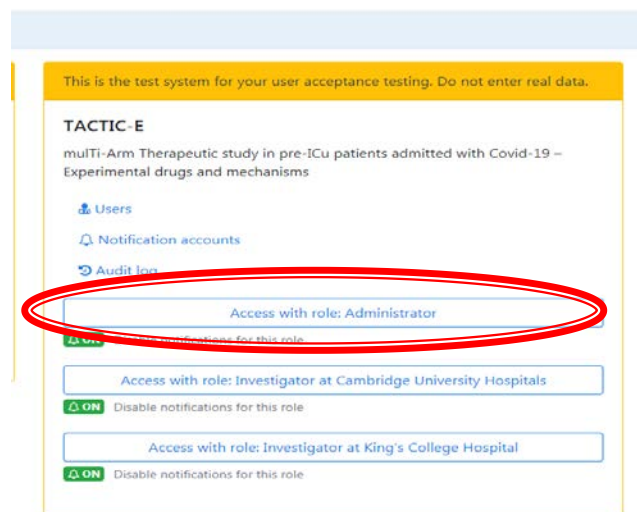
This ID will be used to identify the patient in all documents throughout the trial

Randomisation

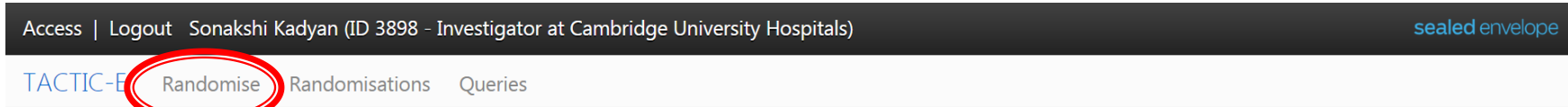
- ▶ Randomise patient at the **end of baseline** visit
- ▶ Investigators delegated to randomise participants will be given a log-in and a link to access Sealed Envelope (randomisation system)
- ▶ www.sealedenvelope.com/access/
www.sealedenvelope.com/redpill/tactice
- ▶ When you have been setup you will receive an email with a link to Sealed Envelope and your login details
- ▶ You will be prompted to change your password on your first login

Randomisation

1. Click on role as Investigator in the middle of the display screen to randomise a patient



2. Click on randomise



TACTIC-E

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

Randomisation

- ▶ Enter information required by the randomisation system
- ▶ Subject ID (participant unique trial ID e.g. Nxx-0001)
- ▶ Partial participant DoB (Month/Year)
- ▶ Initials XXX
- ▶ Date of informed consent
- ▶ A check against drug specific exclusion criteria for EDP1815/Ambrisentan + Dapagliflozin ([image on next slide](#))
- ▶ Confirmation that participant meets all inclusion criteria (Yes/No)
 - ▶ Confirmation that written informed consent has been obtained (Yes/No)
 - ▶ Confirmation that none of the exclusion criteria apply (Yes/No)
 - ▶ Site (drop-down menu, only your site will show)

Randomisation

Randomisation

Subject ID*

Initials*

2 or 3 letters

Month and year of birth*

mm/yyyy

Date of informed consent*

dd/mm/yyyy

Patient is taking a systemic immunosuppressive agent such as, but not limited to, oral steroids, methotrexate, azathioprine, ciclosporin or tacrolimus, unless these are given as part of COVID standard of care treatment*

- Yes
 No

Type 1 diabetes*

- Yes
 No

Known idiopathic pulmonary fibrosis*

- Yes
 No

Previous hospital admission with ketoacidosis*

- Yes
 No

History of symptomatic heart failure within 3 months of admission*

- Yes
 No

Sustained blood pressure below 90/60 mmHg at admission*

- Yes
 No

Metabolic acidosis defined as pH < 7.25 (or venous bicarbonate < 15 mmol/l) AND ketones > 3.0 mmol/L*

- Yes
 No

Alanine transaminase and/or aspartate transaminase (ALT and/or AST) > 3 times the upper limit of normal (only one needs to be measured)*

- Yes
 No

Inclusion criteria

Does the subject meet all inclusion criteria?*

- Yes
 No

Has written informed consent been obtained?*

- Yes
 No

Exclusion criteria

Do any of the exclusion criteria apply?*

- Yes
 No

Notes

Apps

Do any of the exclusion criteria apply?

No

Notes

-

Investigator's declaration

By entering my password below I declare that the information presented in this form accurately reflects the medical records, including the results of tests and evaluations performed on the dates specified.

Name
Sonakshi Kadyan (ID 3898 - Investigator at Cambridge University Hospitals)

Date
22 Jun 2020

Password

[Back](#)

The randomiser will then be asked to re-enter their password to confirm

⚠ This is a test system - use for evaluation purposes only!

Access | Logout | Sonakshi Kadyan (ID 3898 - Investigator at Cambridge University Hospitals) sealed envelope

TACTIC-E Randomise Randomisations Queries


Subject ID N01-0007 | N01: Cambridge University Hospitals, United Kingdom

[Return to subject](#) [Create a query](#)

Randomisation

The subject was successfully randomised.

Randomised to **EDP1815** at 22 Jun 2020



Success

Randomised to **EDP1815** at 22 Jun 2020 17:35 BST

[OK](#)

Randomisation

Subject ID
N01-0007

Initials
CWG
2 or 3 letters

Month and year of birth
06/2002
mm/yyyy

Date of informed consent
22/06/2020
dd/mm/yyyy

Patient is taking a systemic immunosuppressive agent such as, but not limited to, oral steroids, methotrexate, azathioprine, ciclosporin or tacrolimus, unless these are given as part of COVID standard of care treatment
No

Screen when randomisation is successful.

Randomisation

- ▶ After a successful randomisation, an arm will be assigned to the patient. This will need to be added to the CRF

- ▶ The following personnel will receive an email confirming the randomisation arm:
 - TACTIC-E Lead Site Trial office
 - Randomiser
 - Investigators at the randomising site (if delegated to randomise at the site)
 - Pharmacy at site (notification account)

- ▶ Email notification should be printed and filed in the ISF

Further information on randomisation can be found in the TPM



Evaluating new drugs against COVID-19


TACTIC-E

Data Entry / CRFs

Prompt data entry key

AE of special interest

Dapa/Ambri arm
Diabetic ketoacidosis
New peripheral oedema



ADVERSE EVENT OF SPECIAL INTEREST FORM

Participant ID N□□-□□□□

Participant NHS/hospital number (first five digits) □□□□□

Partial DOB (Month/Year) □□/□□□□

AEI No.	AEI type* (details on reverse side)	Date of onset (DD/MMM/YY)	Date of resolution (if applicable) (DD/MMM/YY)	Days from admission to AEI	Outcome ^b	Severity ^c	Is the AEI serious? ^d	Is the AEI related to the IMP? ^e
		□□/□□□/□□	□□/□□□/□□					
		□□/□□□/□□	□□/□□□/□□					
		□□/□□□/□□	□□/□□□/□□					
		□□/□□□/□□	□□/□□□/□□					
		□□/□□□/□□	□□/□□□/□□					
		□□/□□□/□□	□□/□□□/□□					

^aAEI type

1 = New diabetic ketoacidosis in those patients on Dapagliflozin and Ambrisentan

2 = New peripheral oedema in those patients on Dapagliflozin and Ambrisentan

^bOutcome

1 = Resolved, no residual effects

2 = Resolved, with residual effects

3 = On-going

4 = Death

^cSeverity

1 = Mild

2 = Moderate

3 = Severe

^dIs the AEI serious?

1 = Results in death

2 = Is life-threatening

3 = Requires hospitalisation

4 = Results in persistent or significant disability

5 = Results in congenital anomaly or birth defect

6 = Medically significant

7 = Non-serious

^eIs the AEI related to the IMP?

1 = Unrelated

2 = Unlikely

3 = Possibly

4 = Probably

5 = Definitely

PI or designee: (name)

PI or designee: (signature)


Date: □□/□□□□/□□□□

Scan form and email **immediately** to: cambs.cardiovascular@nhs.net & include Trial name and 'AEI' in subject header; also inform UK lead site coordinator

TACTIC-E
ADVERSE EVENT OF SPECIAL INTEREST FORM

Page □□ of □□

Version 2.0
13/AUG/2020



Participant ID N□□-□□□□

Partial NHS/hospital number (first five digits) □□□□□

Partial DOB (Month/Year) □□□/□□□□

DAYS 3, 6, 14, DISCHARGE (IN-HOSPITAL ASSESSMENTS)

BLOOD GASES

Venous blood gas **must** be performed at this visit before dosing in participants randomised to Ambrisentan and Dapagliflozin:

Is the participant randomised to Ambrisentan and Dapagliflozin? Yes No

If 'No', skip this section

If 'Yes':

Venous pH: □.□□ □□/□□□□/20□□

If venous pH < 7.3 and ketones > 3.0 mmol/L, complete the TREATMENT CESSATION FORM. Complete the ADVERSE EVENT OF SPECIAL INTEREST FORM and scan and submit immediately by email to cambs.cardiovascular@nhs.net and inform the UK lead site coordinator

Venous HCO₃: □□.□ □□/□□□□/20□□
mmol/L

If venous HCO₃ < 15 mmol/L and ketones > 3.0 mmol/L, complete the TREATMENT CESSATION FORM. Complete the ADVERSE EVENT OF SPECIAL INTEREST FORM and scan and submit immediately by email to cambs.cardiovascular@nhs.net and inform the UK lead site coordinator

BLOOD KETONES

The following test **must** be performed at this visit point of care (POC) before dosing in participants randomised to Ambrisentan and Dapagliflozin:

Is the participant randomised to Ambrisentan and Dapagliflozin? Yes No

If 'No', skip this section

If 'Yes':

Ketones: □□.□ mmol/L □□/□□□□/20□□

If ketones > 3.0 mmol/L and either venous pH < 7.3 or venous HCO₃ < 15 mmol/L, complete the TREATMENT CESSATION FORM. Complete the ADVERSE EVENT OF SPECIAL INTEREST FORM and scan and submit immediately by email to cambs.cardiovascular@nhs.net and inform the UK lead site coordinator

TACTIC-E
DAYS 3, 6, 14, DISCHARGE
(IN-HOSPITAL ASSESSMENTS)

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Version 2.0
13/AUG/2020

Data entry

- ▶ Paper CRFs provided currently
- ▶ Guidance/instructions in Trial Procedures Manual

e-CRFs will be available soon to be used instead of paper CRF

-- Training/instruction will be provided--

Planned Interim Analyses

- ▶ *n=10 per arm*: Review safety
- ▶ *n=30 per arm*: Variance of biomarkers (CRP, NLR, Ferritin, DDimer, LDH) + safety
- ▶ *n=100 per arm*: Biomarker futility endpoint + safety
- ▶ *n=125 per arm*: Clinical futility endpoint + safety
- ▶ *n=229 per arm*: Repeat Clinical futility endpoint + safety
- ▶ *n=469 per arm*: Repeat Clinical futility endpoint + safety



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Questions?



Evaluating new drugs against COVID-19

TACTIC-E Pharmacy

Trial Drugs

In accordance with the CTA granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) the following medications are classed as Investigational Medicinal Products (IMPs) within this trial.

- EDP1815 oral 8 x 10¹⁰
- Ambrisentan tablets
- Dapagliflozin tablets

Trial Drugs

IMP	Route	Formulation	Strength(s)	Storage Requirements	Supply
EDP1815	Oral	Capsule	8 x 10 ¹⁰ cells per capsule in a carton of 70 capsules, containing 7 blisters of 10 capsules each	Store in the refrigerator between 2 – 8°C in the original container Protect from light	Clinical Trial Supply by Sponsor (Supplied by Evelo free of charge)
Dapagliflozin	Oral	Tablet	10mg film coated tablets in blister packs containing 28 tablets commercial product will be supplied	Room temperature below 25°C in the original container	Commercial product supplied by Sponsor (Supplied by Astra Zeneca free of charge)
Ambrisentan	Oral	Tablet	5mg film coated tablets	Room temperature below 25°C in the original container <u>OR</u> as per SmPC for brand used	Hospital local supply (reimbursed by Sponsor for the amount used) No specific brand is required

DOSING SCHEDULE

IMP	Dose	Dose Frequency	Route of administration	Other requirements	Dispensing
EDP1815	16 x 10 ¹⁰ cells (2 capsules) TWICE a day for up to 7 days (increased to 14 days if required)	2 capsules TWICE a day for up to 7 days (increased to 14 days if required) or until discharge. DO NOT continue on discharge	Oral in fasted state. It should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal.	Sites should dispense 3 blisters of 10 capsules for 7 days' supply of study medication	Attach dispensing label as per local procedure. Ensure it is kept in a fridge on the ward (use within 24hr at room temperature)
Dapagliflozin	10mg	ONCE a day up to a maximum of 14 days or until discharge. DO NOT continue on discharge	Oral can be taken with or without food	On receipt affix annex 13 compliant label and ring fence supplies – sample label provided in pharmacy manual	Additional dispensing label with instructions can be added as per local procedure
Ambrisentan	5mg	ONCE a day up to a maximum of 14 days or until discharge. DO NOT continue on discharge	Oral can be taken with or without food.	Dispense 7 days supply at a time . Do not require annex 13 compliant label (No requirement for ring fencing the medication)	Dispensing label with instructions required

All patients within this trial will be inpatients, please ensure that patients are identified as being on the trial and that the trial medication supplied is used .

This treatment will be in addition to standard of care treatment for these patients.

SAMPLE LABELS

Dapaglifozin or Ambrisentan
Sample Label Or label with
instructions can be added
when dispensing

EDP1815 Sample Label
each blister of 10 capsules
will contain this label

For Clinical Trial Use Only

TACTIC-E trial

EudraCT No: 2020-002229-27

Sponsor: Cambridge University Hospitals NHS Foundation Trust

Local Site Name:.....

TACTIC-E STUDY (EDP1815-204)

Participant ID:.....

Batch Number:.....Expiry Date:.....

This wallet contains 10 enteric-coated capsules for oral administration of

EDP1815 8.0 x 10¹⁰ cells/capsule

Take as directed by your doctor

Store refrigerated between 2°C and 8°C

For clinical Trial use only

Investigator:.....

Dosing Modifications

Drug	Starting Dose	Dose level -1	Other instructions
EDP1815	2 capsules TWICE a day	No dose adjustments planned	Patients should not be on any immunosuppressive agents
Dapagliflozin	10mg ONCE a day	No dose adjustments planned	STOP treatment if metabolic acidosis occurs defined as Venous pH < 7.3 (or venous bicarbonate < 15 mmol/l) AND ketones > 3.0 mmol/L
Ambrisentan	5mg ONCE a day	No dose adjustments planned	

Drug Interactions

Dapagliflozin

- may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension

EDP1815

- no anticipated drug–drug interactions

Ambrisentan

- There is a lack of inductive effect of Ambrisentan on the CYP3A4 isoenzyme

Trial Drug Accountability

It is the responsibility of the Clinical Trial Pharmacy Lead at each Site to maintain drug accountability records for all 3 Study medications

- ▶ Accountability Log(s) are provided for the trial; however, sites can use their own logs
- ▶ If using sites own logs then copies must be made available to Tactic-E co-ordinator upon request
- ▶ This is an open label trial
- ▶ **Sealed Envelope** randomisation system will be used for allocation of the drug (see earlier randomisation section and TPM)

Ordering of EDP1815 and Dapagliflozin

Initial Orders

- ▶ The TACTIC–E co-ordinator will order the initial supply of study medications for each site upon opening to recruitment.

Subsequent orders

- ▶ It is the site pharmacy's responsibility to maintain adequate stocks of IMP. Sufficient supplies should be ordered by sites as needed in conjunction with the lead site coordinator, in order to meet the requirements of the trial population.
- ▶ Please ensure that sufficient time is allowed for delivery when requesting to place new orders.
- ▶ Sites must ensure the stock is within date and there is stock rotation of supplies to ensure the shortest expiry dates are used first. To minimise delivery costs, it is recommended that pharmacies order their stock on a quarterly basis.

Ordering process for Dapagliflozin and EDP1815

- ▶ Request an Order with the TACTIC-E trial lead site coordinator
- ▶ Ensure that you provided site delivery address correctly.
- ▶ Email the Tactic-E Trial Co-ordinator with your request.
- ▶ File a copy of the correspondence in the relevant section of the PSF.
- ▶ Please allow up to 5 – 7 working days for delivery of the drug.

Ordering of Ambrisentan

- Locally supplied study medication

- Sponsor will re-imburse for the amount used within this trial

- It is the site pharmacy's responsibility to maintain adequate stocks of IMP. Sufficient supplies should be ordered by sites as needed, in order to meet the requirements of the trial population.

- Please do not over-order

IMP Destruction of Dapagliflozin

- ▶ Destruction of all unused or expired medication, may only be undertaken after written permission has been obtained from the sponsor (Tactic-E lead site co-ordinator)
- ▶ This destruction must be recorded on the Drug Destruction Log and the Accountability Log for each study medication to ensure the running balance is accurate.
- ▶ The completed logs and the confirmation of 'permission to destroy' email should be filed in the Tactic-E PSF. Supplies must be destroyed as per local destruction policies and procedures.
- ▶ Sites are permitted to use their own destruction log but this must ensure all the information required by the sponsor is available on the forms.

Patient returns

- ▶ Destruction of **patient surplus study medication** can occur at the site as per local procedure. No returns are expected to be sent to pharmacy
- ▶ Note: Authorisation is not required for patient returns destruction

IMP Destruction of EDP1815

1

- EDP1815 should not be destroyed at site UNLESS the site is able to produce a certificate of destruction/local SOP for destruction processes and this is approved by Evelo. *Discuss with UK Sponsor coordinator to facilitate this*

2

- All unused, expired stock and patient returns should be sent back to the Evelo

3

- Sites should ensure all accountability for EDP1815 is completed and reconciliation of all drug has occurred before requesting to arrange a courier for collection.
- Details will follow on how to manage returns

TEMPERATURE EXCURSIONS of IMPs

1

- In case of temperature excursion the site must quarantine the IMP immediately under the correct storage conditions and as per local site procedure (if the IMP has been stored incorrectly by the participant it should be retrieved from the participant and a new supply should be dispensed)

2

- The site must contact the TACTIC-E trial co-ordinator to inform of the temperature excursion or damage (giving the following information: dates, duration, and minimum/maximum temperatures as appropriate (including a temperature trace or printout where possible) quantity of packs and batch number of affected stock).

3

- No affected IMP is to be given to participants until final decision and instruction is received from the TACTIC-E co-ordinator.

Pharmacy Monitoring

1

- Site Self-Assessment Monitoring / Central Monitoring

2

- A request will be sent to the site pharmacy periodically, by TACTIC-E Trial co-ordinator for drug accountability records

3

- Review of pharmacy site file (checklist provided periodically by TACTIC-E Trial co-ordinator)



TACTIC-E

Pharmacovigilance: Safety Data Management

Evaluation of Safety Data: AEs, AR,SAEs, SARs, SUSARs

Seriousness Assessment

- Refer to the protocol section 11.1.4

Causality Assessment

- Refer to the protocol section 11.3.2

Expectedness Assessment

- Refer to the protocol RSI– protocol section 11.1.6:
- *[Section 4.8 of the SmPC Forxiga \(Dapagliflozin\), dated 02 Jan 2020](#)*
- *[Section 4.8 of the SmPC Volibris \(Ambrisentan\), dated 12 Nov 2018](#)*
- *[Section 8 of EDPI815 Investigator’s Brochure Version 2.1 dated 28 January 2020](#)*

Severity Assessments

- Refer to the protocol section 11.3.3

TACTIC–E AEs Collecting/Recording Details

Adverse events will be collected & assessed:

- *From: the point of Informed Consent*
- *To: 90 (+/- 7 days) days after the baseline visit.*

Adverse events will be recorded:

- *AEs – in medical notes only*
- *ARs – in the medical notes and the CRF and/or AR log.*
- *All SAEs – in the **study specific SAE reporting form***

The following AEs will be recorded as AESI using study specific CRF:

- *Diabetic ketoacidosis– for patients on Ambrisentan & Dapagliflozin*
- *New peripheral oedema –for patients on Ambrisentan & Dapagliflozin arm*

TACTIC-E SAEs Reporting Details

SAEs & SARs will be reported within 24 hours:

- *SAEs & SARs* – since site awareness date to the CI / Coordination Team
- *SARs* – since CI/Coordination Team notification to Sponsor

AESI reporting details:

- *ALL PIs must report all AESIs to the CI in a timely manner*
- *Serious AESI should be reported following procedure for an SAE reporting*

SAES, SARs, SUSARs for the Dapglifozin/Ambrisentan arm should ALSO be reported to:

- *ASTRAZENECA via:*
AEMailboxClinicalTrialTCS@astrazeneca.com
- *Medpace via: safetynotification@medpace.com.*

TACTIC-E Pregnancy Reporting Requirements

Pregnancy (study participant or participant's partner) will be reported until the 3 month follow-up visit

Pregnancy should be reported within 24 hours of site awareness to:

*The Chief Investigator/
Trial Coordination team*

The Sponsor

Pregnancy complications will be reported as SAE/SAR or SUSAR

- Spontaneous abortion
- Induced abortion (due to clinical/ foetal developmental reason)

- Still birth
- Neonatal death
- Birth defect(s)

TACTIC-E

Pregnancy Reporting Form

TACTIC-E
Evaluating new drugs against COVID-19

Final Version 1.1 Date 11August2020

Please complete details of any pregnancies from the time of informed consent. For guidance on which events to report please refer to the protocol.
Please scan and email this form to the Coordination Centre within 24 hours of awareness.

Trial Details				Participant Details						
Trial Title:	TACTIC-E			Initials:	□□□□		Participant Trial No:	□□□□□□□□		
Sponsor R&D No:	A095607			Date of Birth:	□□/□□/□□	□□/□□/□□	Pregnancy Ref. No:	□□□□□□□□		
EudraCT No.	2020-002229-27				d d	m m	y y			
Further Trial Participant Details				Report Details						
Gender:	<input type="checkbox"/> Male <input type="checkbox"/> Female			Type of Report:	<input type="checkbox"/> Initial Report <input type="checkbox"/> Follow Up Report		Centre:	□□□□□□□□		
							Name of person reporting:	□□□□□□□□		
Pregnant Partner Details				Contraception used (Both Trial Participant and Partner)						
Date of Birth:	□□/□□/□□			Mother has consented to pregnancy monitoring:	<input type="checkbox"/> Yes <input type="checkbox"/> No		□□□□□□□□			
	d d	m m	y y				Pregnant Females Weight in kg	□□□□		
Treatment details								<input type="checkbox"/> Tick if no trial treatment received		
IMP(s) trial participant received (if applicable)	Dose	Units	Freq. (d/d)	Route of Admin. (Use codes)	Date of first dose	Action taken (Use codes)	Date of last treatment given prior to conception	End date of trial treatment (if applicable)	Name of person making decision on action taken	
EDP1815	2	CAPSULES	BD	oral	□□/□□/□□		□□/□□/□□	□□/□□/□□		
Dapagliflozin	10	mg	QD	Oral	□□/□□/□□		□□/□□/□□	□□/□□/□□		
Ambrisentan	5	mg	QD	Oral	□□/□□/□□		□□/□□/□□	□□/□□/□□		
					d d	m m	y y	d d	m m	y y
Codes: Action taken: 1 = None 2 = Treatment Delayed 3 = Drug stopped permanently 4 = Unknown										
Please ensure you are using the current version of this document. Please notify any changes required to the relevant QA Manager This document is reviewed and updated in line with emerging evidence or local requirements at least every three years										
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TACTIC-E Monitoring

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is **conducted, recorded, and reported** in accordance with the **protocol, SOPs, GCP, and the applicable regulatory requirement(s)**

Trial monitoring is an Integral Component of trial quality assurance process, and critical for GCP fulfilment.

Key monitoring activities

-- Participating Site: Remote Monitoring --

- Conducted approximately every 12 months from site activation

Logistics

- Remote monitoring will be initiated with site's PI in advance
- The site will be instructed to complete a remote monitoring form and questionnaire/checklist tailored to the TACTIC-E trial (provided by CTC).
- The site will have 4 weeks to return the completed form/checklist
- The CTC will provide the site with a report containing details of any findings and required actions to be taken by the site. These actions must be addressed within 4 weeks.

Site staff who complete remote monitoring tasks must be listed to do so on the delegation log

Trial team's involvement in monitoring visits

- **Preparation**

- Ensuring all logs are up to date, including but not limited to screening/approach/subject ID logs, Delegation log, non-compliance log/forms, file note log etc.
- Check filing is up to date and that findings from previous reports have all been addressed
- Ensure all data is entered into CRFs/eCRFs

The frequency of remote monitoring may change depending upon the rate of patient recruitment at the site, quality of the data and the findings from previous monitoring visits

**If it wasn't documented,
it wasn't done!**

**Document what is done as
well as what is not done**

Thank you

Questions?



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