NIHR | Cambridge Biomedical Research Centre

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

Site Initiation Visit: <date>; <time>

UK Site name/ Number: / Nxx

PI: <name>

TACTIC E

*E*valuating new drugs against COVID-19

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

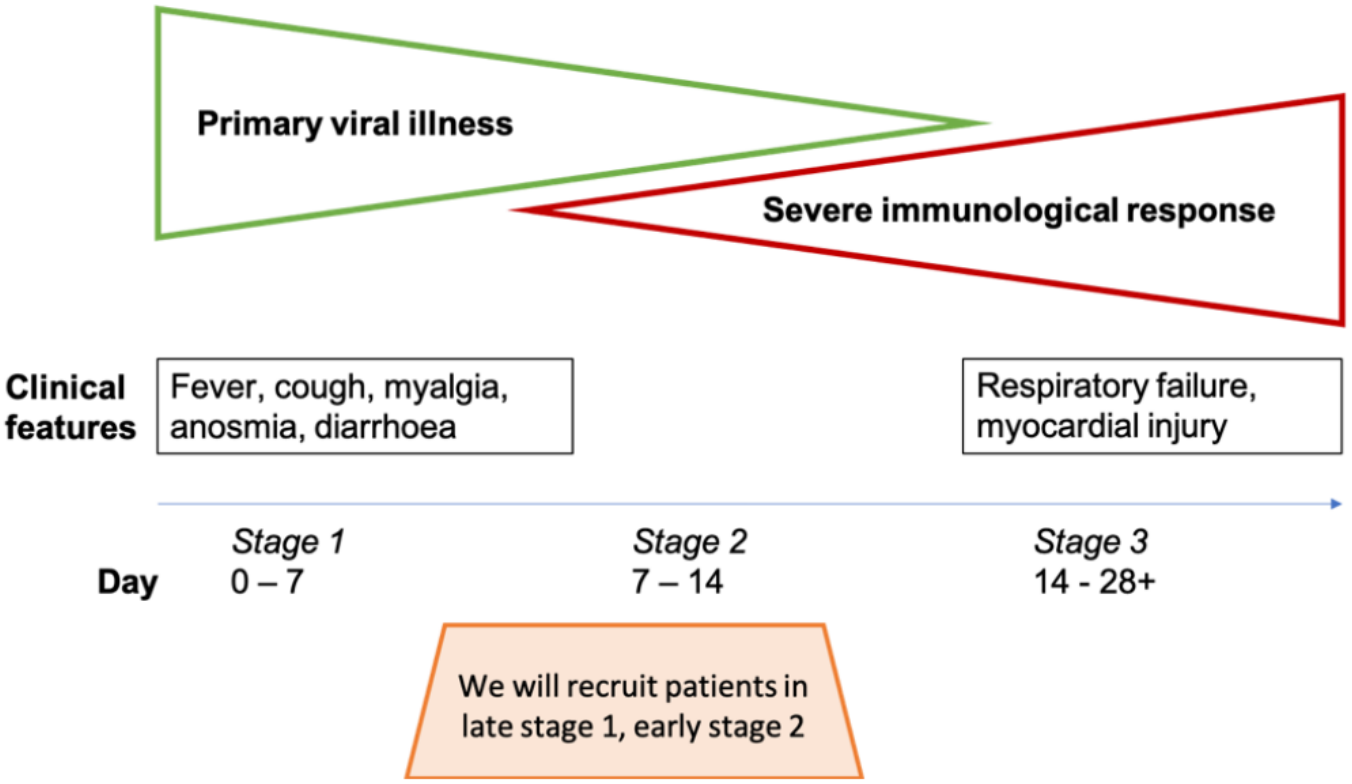
- Sponsor: Cambridge University Hospitals NHS Foundation Trust, UK
- EudraCT Number: 2020-002229-27
- REC reference: 20/WM/0169
- IRAS project ID: 283769
- Funding and drug supply: Astrazeneca and Evelo-Biosciences

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

TACTIC-E
Trial Design and Objectives

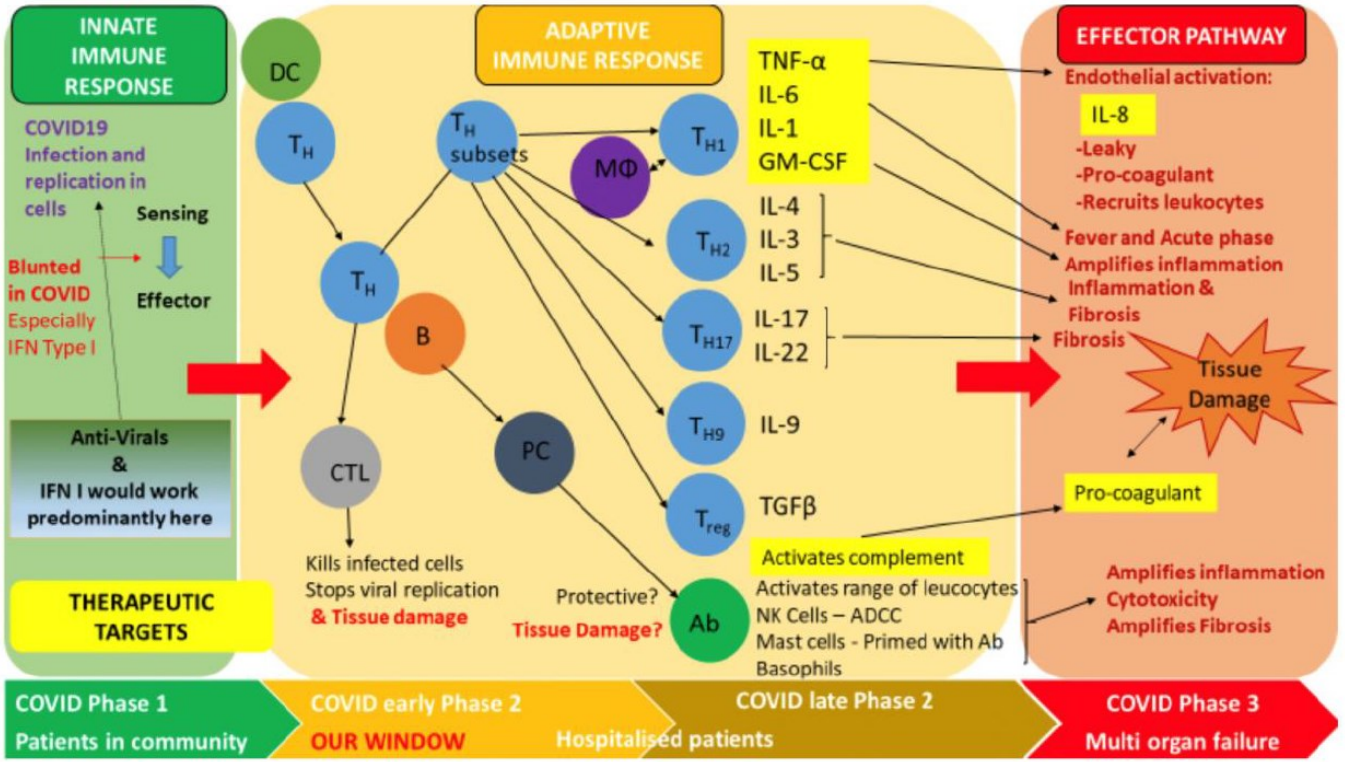
TACTICE
Evaluating new drugs against COVID-19

Stages of COVID-19-related Disease



COVID19 – adaptive immune response to hyperinflammation

- No evidence based Rx from RCTs apart from Dexamethasone (RECOVERY trial) suggesting immunomodulation may be important



COVID19 – pulmonary shunting

- COVID19 presentations depend on the interaction of 3 factors:

(1) the severity of the infection, the host response, physiological reserve and comorbidities;

(2) the ventilatory responsiveness of the patient to hypoxemia;

(3) the time elapsed between the onset of the disease and the observation in the hospital.

2 primary "phenotypes":

Type L, characterized by Low elastance (i.e., high compliance), Low ventilation-to-perfusion ratio, Low lung weight and Low recruitability

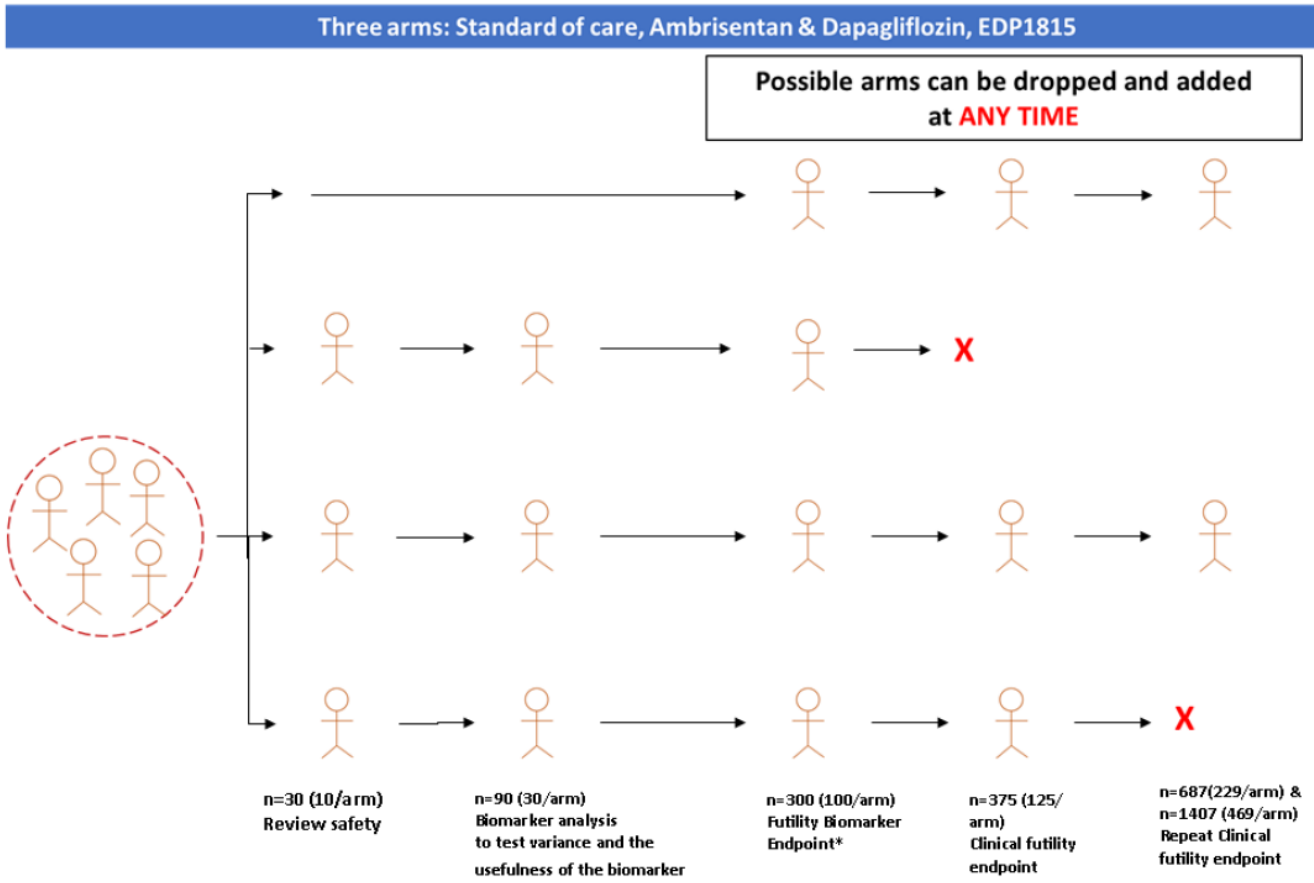
Type H, characterized by High elastance, High right-to-left shunt, High lung weight and High recruitability.

Type L involves pulmonary shunting and hypoxaemia – our hypothesis is this, in part, potentially implicated by endothelin and may offer additional opportunity for intervention with ET blockade

Gattinoni L et al Int Care Med 2020:46;1099-1102

Platform design

TACTIC-E Trial design



*if a useful biomarker has been identified

WEEKLY MONITORING OF SAFETY PROFILES

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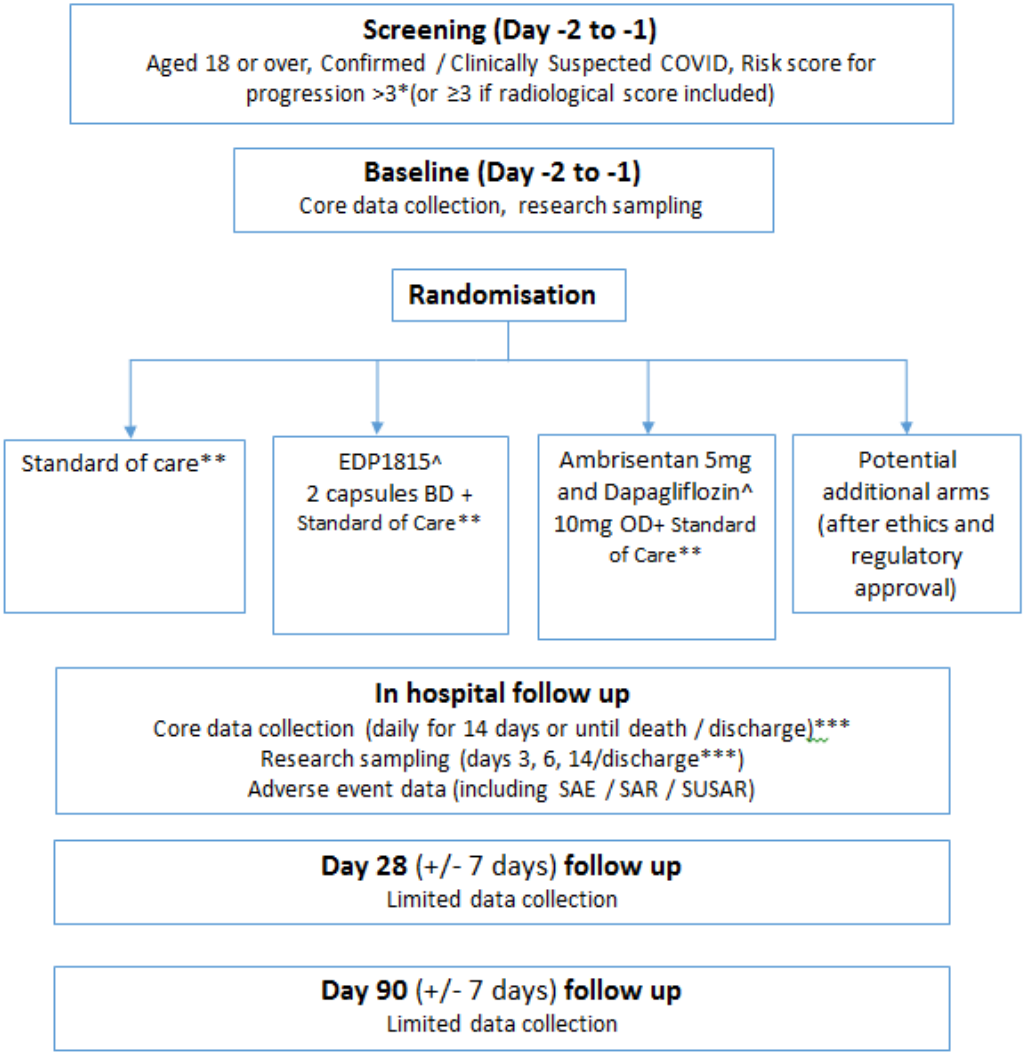
Design



TACTIC-E
Evaluating new drugs against COVID-19

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
Evaluating new drugs against COVID-19

TACTIC-E Secondary objectives

	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

- 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

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-1β, IL-10, IL-17, IL-13

  b. Dapaglifozin and Ambrisentan: serum/plasma ET-1, TNF

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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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 Sp02 >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)

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

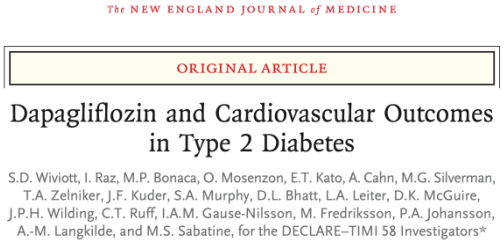
- Shown to reduce risk of worsening HF and mortality in those with Heart Failure with reduced ejection fraction (DAPA-HF trial) irrespective of presence of diabetes
- DECLARE trial: In T2 Diabetics, dapaglifozin showed no difference to placebo in MACE but did result in lower CV death or hospitalisation for heart failure
- Well absorbed, Max concn after 2 hours, oral bioavailability 78%, t½ = 13 hours
- When used with insulin or insulin secretagogue, consider reduction in insulin/sulphonylurea dose to reduce risk of hypoglycaemia
- Dapagliflozin retarded progression to renal impairment in diabetics and non-diabetics


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

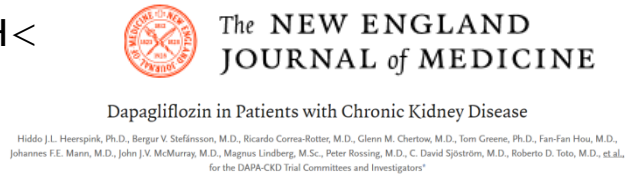
J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*


The NEW ENGLAND JOURNAL of MEDICINE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., et al., for the DAPA-CKD Trial Committees and Investigators*


BMC Medicine

Research article | Open Access | Published: 16 November 2020

Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study

-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
- Heerspink et al. J New Eng Med 2020; 3383:1436-1446

Ambrisentan

Rationale for use in TACTIC-E :

- Ambrisentan is a selective endothelin receptor A antagonist
- lung compliance - reduce the activity of ET-1 at the ET-A receptor leading to a reduction in pulmonary shunting to hypoxic areas of the lung and blunting of inflammatory activity)
- t½ 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

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

Ambrisentan & Dapagliflozin Arm
Adverse Events of Special Interest (AESI)

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

- Diabetic ketoacidosis
- New peripheral oedema

Bicarb/ph + ketones Tests

- For first dose on Day 1, results for bicarb/ph + ketones for that particular day must be reviewed prior to starting the first dose

- Day 2 onwards, bicarb/ph + ketones can be done and reviewed anytime on those days as long as there is a result every day and this is reviewed before dosing is continued the next day. **Do not interrupt dosing on that day to wait for these results.**

Nb. treatment arm is not known prior to randomisation so bicarb/ph + ketones should be done for all patients consented to trial, if patent is then randomised to the Ambri & Dapa arm bicarb/ph + ketones is done daily as detailed above

Reporting the AESI

- Add AESI to eCRF
- Trial coordinator/CI alerted as soon as possible after site awareness
- email cambs.cardiovasular@nhs.net Email subject header: TACTIC-E, AESI, <site name>
- FOR DETAILS REFER TO PV SIV SLIDES and PROTOCOL/TPM

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.1.6x10^{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

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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 x 10^9/L
- Age >40 years
- CRP >40 mg/L

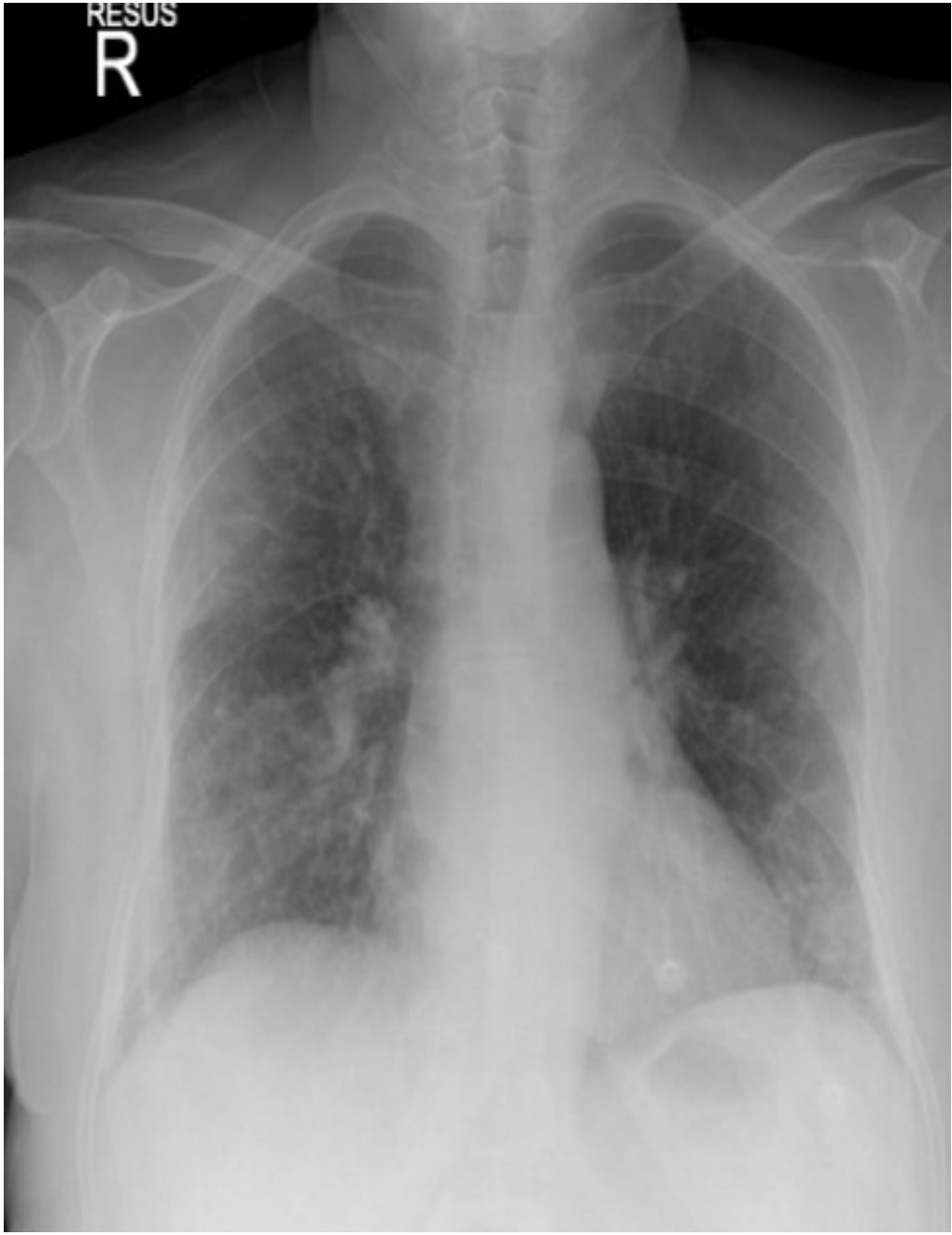
Data derived from first 200 patients admitted to King's College Hospital
adapted from Galloway et al, 2020 submitted

TACTIC E
Evaluating new drugs against COVID-19

Radiographic Severity Score

Score 0-8.
Score each lung separately.

0 = normal
1 = <25% infiltrate
2 = 25-50%
3=50-75%
4=>75%

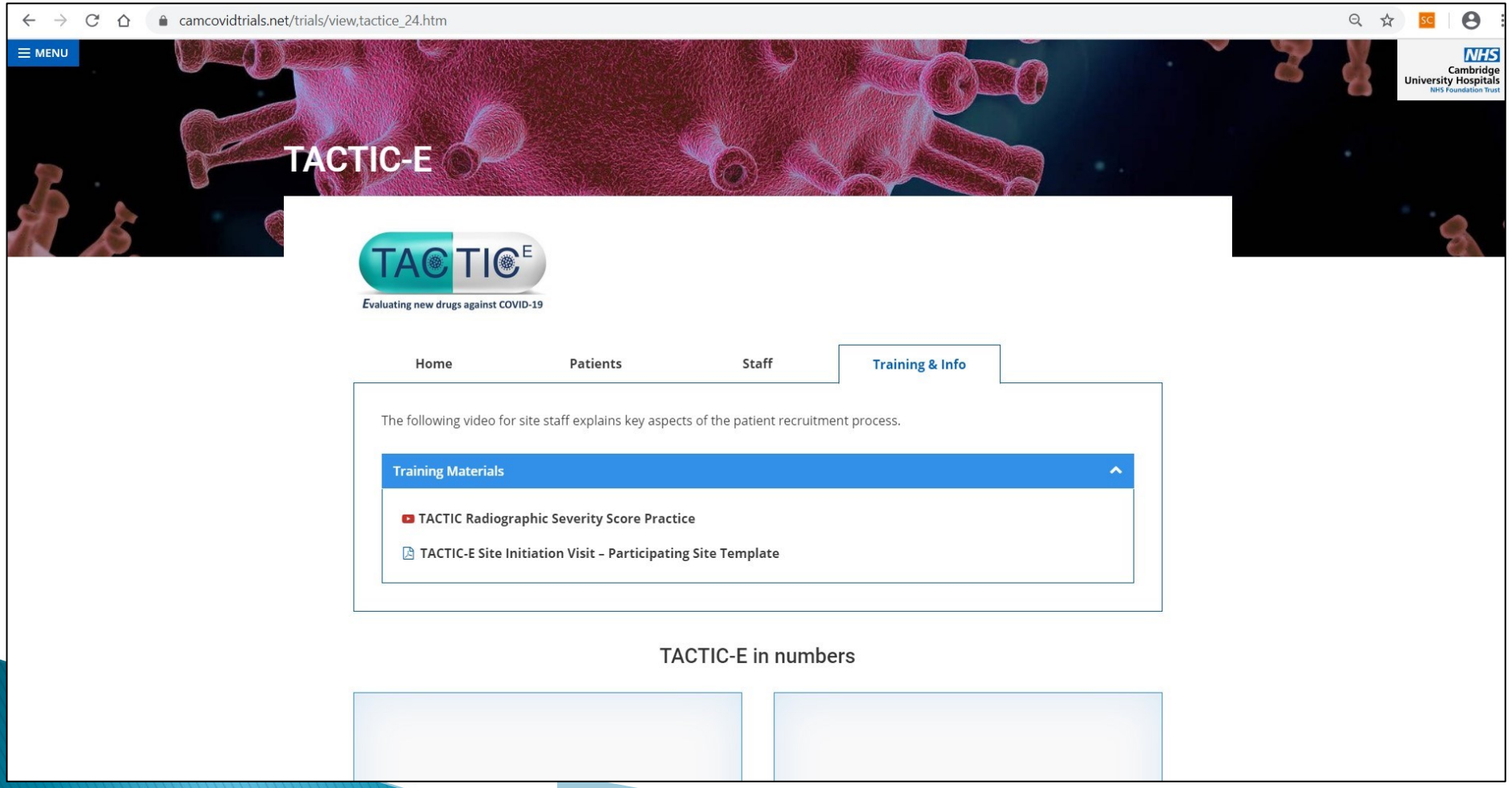


Radiology. 2019 Mar 27:201160

Radiographic Severity Score

Training available online on TACTIC-E website

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



TACTIC E
Evaluating new drugs against COVID-19

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)

*Bicarb/ph + ketones Tests (Dapagliflozin and Ambrisentan arm)

For first dose on Day 1, results for bicarb/ph + ketones for that particular day must be reviewed prior to starting the first dose

Day 2 onwards, bicarb/ph + ketones can be done and reviewed anytime on those days as long as there is a result every day and this is reviewed before dosing is continued the next day. **Do not interrupt dosing on that day to wait for these results.**

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.

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

- 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

Professional Legal Representative

- 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 nominates by the healthcare provider

TACTICE
Evaluating new drugs against COVID-19

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)[#d]	x																x[e]
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	

Screening, Baseline and D1may occur on the same day as long as assessments have been completed and reviewed beforehand

Schedule of Assessments Cont

Biomarker tests[a]* (section 10.5.3) Protocol mandated: FBC (for neutrophil:lymphocyte ratio), CRP, Ferritin, DDimer, LDH, and optionally (where sites are capable) via a plasma store: IL-6, IL8. IL1β, IL-10, IL-17, IL-13, Endothelin-1, TNF		x			x			x							x	
Research blood sampling/venous endothelial cells [a,b,f]		x			x			x							x	x
Venous blood gas (pH) or venous bicarbonate: Screening for all patients & thereafter for Ambrisentan + Dapagliflozin arm only	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood ketone POC: Screening for all patients & thereafter for Ambrisentan + Dapagliflozin arm only	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Review of adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Discharge status																	x
Return to normal function status (ECOG and MRC Dyspnoea scores)																	x
Mortality status																	x
EDP1815 arm only – drug administration			x	x	x	x	x	x	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	
Ambrisentan and Dapagliflozin arm only – drug administration			x	x	x	x	x	x	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	

[a] Samples could be stored for assays of additional biomarkers of response; including but not confined to immunological and genomic transcriptomic and cellular analyses for future analysis
[b] Research sampling is optional where units have capability – not mandatory
[c] The results of these tests acquired up to 48hr before consent may be used to complete the screening and eligibility process.
[d] A clinically indicated chest X-ray/imaging will be reviewed from the patient's medical record to perform the risk score. This is not a trial mandated procedure.
[e] Treatment can continue beyond 7 days to day 14, at the discretion of the PI or his delegate, if the patient is felt to be clinically responding to treatment, is tolerating treatment, and is judged to be likely to benefit from a longer treatment course. Treatment will cease when the patient is discharged from hospital (even if this occurs before Day 7).
[f] Optional venous endothelial cell collection will only occur at selected UK sites
* For D3, D6 and D14 (+/-2 days): The results of FBC, Cockcroft Gault Creat. Clearance, ALT/AST and CRP acquired within a **96 hour window** may be used
^ Can be performed on the same day

* Endothelial cell sampling – at selected UK sites only. Sites should inform the coordination team if undertaking these

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**

**-only if visit is conduced face-to-face rather than over the phone/remotely

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.

Questions so far?