SFX-01 **t**reatment for **Acute Respiratory Infections** (STAR-Covid19)

Background and Overview

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Background to the Trial 1

- Community-acquired pneumonia is a leading cause of morbidity and mortality in the UK
- There have been no new therapies for managing pneumonia since advent of antibiotics in 1950s
- The global pandemic caused by novel coronavirus SARS-CoV-2, has highlighted the need for new drugs to treat pneumonia
- Development of anti-inflammatory therapies that prevent late stage complications is needed
- Such therapies are likely to be efficacious for a range of acute respiratory infections, including COVID-19
- Patients with pneumonia and suspected COVID-19 are eligible for this trial. Patients do not require a positive COVID-19 test to be eligible

Background to the Trial 2

- The nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) is part of the human natural defence against inflammatory and oxidative stress such as the inflammation that occurs during a severe viral infection
- In animal studies, pharmacological activation of Nrf2 reduces the severity of acute respiratory distress syndrome (ARDS)
- **SFX-01** (stabilised sulforaphane), a drug developed by Evgen Pharma, is an activator of Nrf2
- SFX-01 has been tested in over 130 subjects in clinical trials and is well tolerated with main side effects being GI related and ameliorated by taking after food
- In this study one 300mg capsule of SFX-01 is taken orally per day for 14 days
- This is the first study of the effect of SFX-01 in humans with acute respiratory infections at risk of developing ARDS

Hypothesis

- The trial will test the following hypothesis:

Treatment with SFX-01 in addition to standard care will be superior to placebo plus standard care in achieving improved clinical status in patients initially hospitalized with community acquired pneumonia (including patients investigated for suspected COVID19 infection).

Objectives

Primary objective: To evaluate the clinical efficacy of SFX-01 compared to placebo on top of standard care in adult patients initially hospitalized with community acquired pneumonia.

Outcome measure:

7 point ordinal scale measured on Day 15.

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)
7. Death.

Secondary Objectives

Evaluate the clinical efficacy of SFX-01 relative to standard care in adult patients hospitalized with suspected COVID-19

Outcome measures:

- **Clinical Severity**

Time to an improvement of one category from admission using 7-point ordinal scale.
Participant clinical status on 7-point ordinal scale
Participant change from baseline on 7-point ordinal scale
Proportion of participants showing improvement on 7-point ordinal scale
Mean change in the 7-point ordinal scale

- **National Early Warning Score (NEWS):**

Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
Change from baseline

- **Oxygenation**:

Oxygen free days
Incidence and duration of new oxygen use during the trial

- **Mechanical Ventilation:**

Ventilator free days
Incidence and duration of new mechanical ventilation use during the trial.

- **Hospitalisation**:

Duration of hospitalisation (days).

- **Mortality:**

15 day mortality
28-day mortality

Secondary Objectives

Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm

Outcome measures:

- Cumulative incidence of serious Adverse events (SAEs)
- Discontinuation or temporary suspension of treatment

Exploratory objectives (All sites)

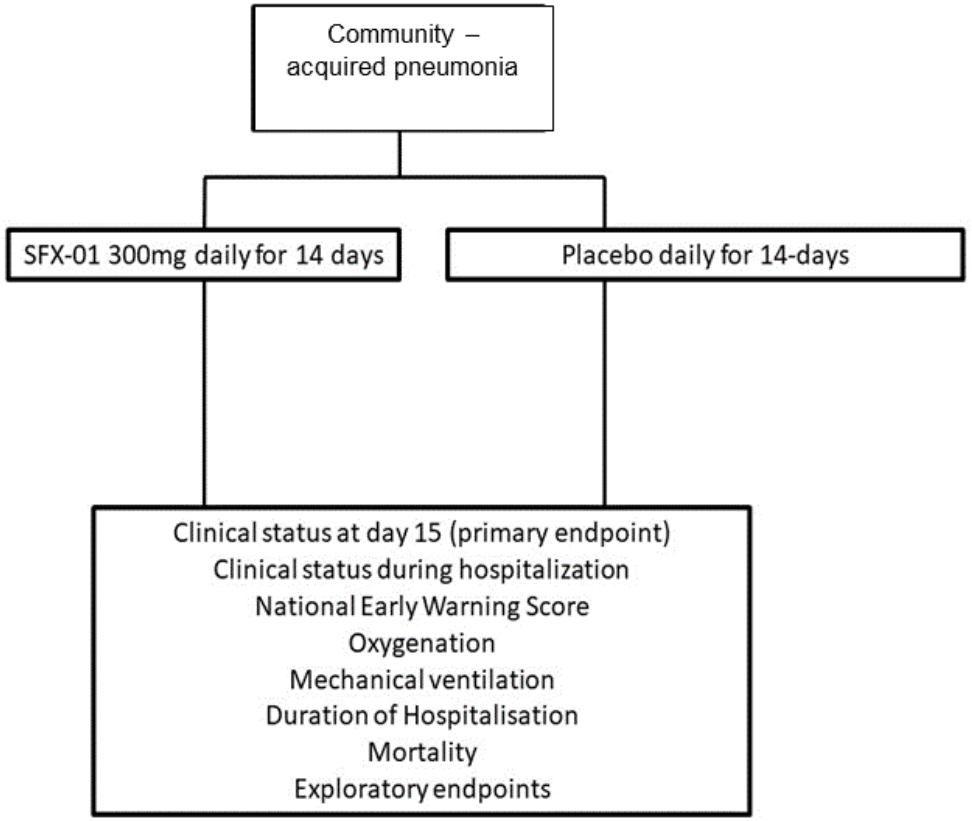
Subanalysis of outcomes according to the causative pathogen

- Biofire analysis of nasal swab or sputum sample

Exploratory objectives (TAYSIDE ONLY)

- Analysis of Nrf2 pathway activity in isolated peripheral blood mononuclear cells
- Neutrophil functional studies in isolated cells
- Measurement of interleukin-6, interleukin-1 beta and TNF-alpha in blood

Trial design



Target 300 participants will be enrolled from participating hospitals and randomized to receive either SFX-01 or placebo

Patients in both arms will receive all other therapies required to manage their condition (standard of care). No concomitant medications will be stopped for trial purposes.

Co-enrolment

- Participants cannot be co-enrolled in other CTMP studies
- Participants can be enrolled in observational studies

Inclusion criteria

- 18 years of age or older
- Community acquired pneumonia (defined as a new radiographic infiltrate on chest x-ray or CT scan in a patient presenting with respiratory symptoms both of which are clinically evident less than 48 hours after hospitalization).
- Tested for suspected SARS-CoV-2 infection via RT-PCR or another approved laboratory method*
- Increased risk of mortality on admission (defined by CURB65 score greater than or equal to 1 or the presence of bilateral radiographic infiltrates)
- Treatment can be commenced within 96 hours of hospital admission
- Requires hospitalisation but NOT requiring mechanical ventilation at randomisation
- Participant (or legally authorized representative) provides written informed consent
- Able to take oral medication at randomisation
- Participant (or legally authorised representative) understands and agrees to comply with planned trial procedures.

*for the avoidance of doubt, this trial permits inclusion of patients presenting with acute respiratory infections whether or not the test for SARS-CoV-2 is positive. Patients can be randomised to the study while awaiting the results of the test for SARS-CoV-2.

Exclusion criteria

- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) greater than 5 times the upper limit of normal, result within 72 hours of randomisation (the result closest to randomisation should be used if several results are available).
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR less than 30), result within 72 hours of randomisation (the result closest to randomisation should be used if several results are available)
- Pregnant or breast feeding.
- Anticipated transfer to another hospital which is not a trial site within 24 hours.
- Hospital-acquired pneumonia (defined as onset of respiratory illness more than 48 hours after admission to hospital)
- Allergy to SFX-01
- Patients in whom active treatment is not considered appropriate.
- Use of any investigational drug within five times of the elimination half-life after the last trial dose or within 30 days, whichever is longer.