Justification of substantial amendment for RECOVERY protocol V22.0

This document is a detailed justification for the changes to the RECOVERY protocol in version 22.0. The change number refers to the Amendment Tool change number included with this amendment.

Change 1: Addition of Paxlovid for adults

Paxlovid is a combination of PF-07321332 (nirmatrelvir) and ritonavir. Nirmatrelvir is a 3-chymotrypsin-like protease inhibitor which inhibits cleavage of polyproteins involved in viral replication.[1] It is co-formulated with ritonavir which inhibits its CYP3A-dependent metabolism and hence increases the plasma concentration of nirmatrelvir. It is approved in the UK for the treatment of adults with COVID-19 who do not required supplemental oxygen and are at increased risk of progression to severe COVID-19.[2]

Its approval is based on the interim analysis of the EPIC-HR trial in which 2246 participants with COVID-19 (symptom onset ≤5 days previously) were randomised to receive Paxlovid (300/100 mg) or placebo twice daily for 5 days. The primary outcome is the proportion of participants with COVID-19 related hospitalisation or death within 28 days of randomisation. In the interim analysis, 8/1037 (0.8%) allocated Paxlovid *vs* 66/1046 (6.3%) allocated placebo.[3] In an interim analysis of 774 participants, adverse events were similar between the two groups: 19% among those allocated Paxlovid *vs* 21% among those allocated placebo. Most were mild; only 1.7% *vs* 6.6% were serious and 2.1% *vs* 4.1% led to discontinuation.[4]

The safety concerns and proposed mitigations are as follows:

1. Spike glycoprotein substitutions and potential resistance: monitoring of SARS-CoV-2 genotype and resistance markers using nasal swab samples collected at baseline, day 3 and day 5. (Please also see 'Design' below.)
2. Potential interaction with high-dose dexamethasone: as ritonavir inhibits metabolism of dexamethasone there is potential for very high plasma concentrations of dexamethasone if ritonavir and high-dose dexamethasone are co-administered. Therefore patients who are eligible for Paxlovid (ie, the drug is suitable and available) will be excluded from the high-dose dexamethasone comparison by the randomisation system (regardless of its suitability and availability) to ensure that such co-administration is not caused by the trial. Paxlovid inhibits CYP3A to a similar extend as itraconazole. Based on this assumption, Paxlovid would increase dexamethasone exposure by 3-4 times (but later induction of CYP3A would reduce this effect), meaning that patients taking 6mg dexamethasone would have similar exposure to patients taking high-dose (20mg) dexamethasone.
3. Interactions with other medicinal products: a list of contraindicated medications (taken from both UK SmPC and US FDA EUA) is included in protocol and will be covered in training materials which local investigators must complete before the comparison is activated at their site. As this study is being conducted in hospital, use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) which will guide modifications to both the study treatment and use of concomitant medication.

Special populations

The primary route of elimination of nirmatrelvir is renal. Patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) will be excluded from the comparison, and patients with moderate renal impairment (eGFR ≥30 <60 mL/min/1.73m^2) should receive a reduced dose of Paxlovid (150/100 mg twice daily).

Patients with severe hepatic impairment (Child-Pugh class C) will be excluded from the Paxlovid comparison.

Pregnant women are not excluded following advice from the UK Teratology Information Service. Their full opinion is included with this application. For other women of child-bearing potential we recommend they avoid pregnancy while taking the medication or for 4 days thereafter. This is to match the guidance given to women of child-bearing potential who receive molnupiravir to avoid confusion. The extra 4 days (not specified in the Paxlovid Summary of Product Characteristics) would not have a material impact and avoids confusing participants about the recommendations.

Design

The Paxlovid comparison is in partial factorial design with other comparisons for COVID-19 ie, empagliflozin, molnupiravir and sotrovimab. This is an important aspect because there are real risks of antiviral resistance developing with monotherapy (as has been observed in other viral diseases). SARS-CoV-2 main protease polymorphisms associated with reduced sensitivity to nirmatrelvir have been identified.[3] Their frequency and clinical significance is not yet known. Cross-resistance between nirmatrelvir and anti-SARS-CoV-2 monoclonal antibodies, molnupiravir or remdesivir are not expected given their different mechanisms of action. Therefore combination therapies may be more appropriate, but these need to be assessed. With the current design it is anticipated that some participants will be eligible (ie, drug is both suitable and available) for just one antiviral, others eligible for two and some for all three. It will therefore be possible to assess each antiviral when given as monotherapy or in combination with other antivirals. These assessments will include clinical efficacy and safety (based on the outcomes pre-specified in the trial protocol), and also genetic viral resistance markers based on nasal swab samples.

Supply

This comparison would only begin once supply is available and agreed with DHSC.

References

1. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. Science 2021;374:1586-93.
2. Regulatory approval of Paxlovid. 2021. (Accessed 13-Jan-2022, at https://www.gov.uk/government/publications/regulatory-approval-of-paxlovid.)
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorisation for Paxlovid. 2021.
4. Pfizer. Summary of Product Characteristics for Paxlovid. 2021.