

Rapid Policy Statement

Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of hospital-onset COVID-19 (Version 7)

Publication date: 30 May 2022

Effective from: 13 June 2022

Commissioning position

Neutralising monoclonal antibodies (nMABs) or antivirals are recommended to be available as a treatment option for COVID-19 through routine commissioning for adults and children (aged 12 years and above) in hospital with COVID-19 infection in accordance with the criteria set out in this document.

- First-line: nirmatrelvir/ritonavir
- Second-line: remdesivir (antiviral)
- Third-line: sotrovimab (nMAB)

Further information on selecting the most appropriate treatment can be found in the Clinical Guide which accompanies this [policy](#).

Combination treatment with an nMAB and an antiviral is **NOT** routinely recommended.

Background

nMABs are synthetic monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing subsequent entry of the virus into the host cell and its replication. This effectively 'neutralises' the virus particle. Antiviral medications inhibit viral replication and prevent progression of infection.

Recent evidence suggests that antivirals and nMABs significantly improve clinical outcomes in patients with COVID-19 who are at high risk of progression to severe disease and/or death. The following products have conditional marketing authorisation for the treatment of patients with COVID-19:

1) Nirmatrelvir/ritonavir

Evidence

[Final results](#) from the EPIC HR trial indicate that the dual oral antiviral nirmatrelvir/ritonavir resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 day of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19 (Hammond et al, 2022).

Marketing authorisation

Nirmatrelvir/ritonavir administered orally has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19. Access to nirmatrelvir/ritonavir in Northern Ireland for this indication is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

2) **Remdesivir**

Evidence

Remdesivir administered intravenously over 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset and had risk factors for disease progression¹, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021).

Marketing authorisation

Remdesivir delivered intravenously has conditional marketing authorisation in the UK for the following indications:

- treatment of COVID-19 in adults and adolescents (aged 12 to less than 18 years and weighing at least 40kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days.
- treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 within 7 days of symptom onset, for a treatment duration of 3 days.

Use of remdesivir under this policy in children aged 12-17 years would be off-label.

3) **Sotrovimab**

Evidence

Interim analysis of the COMET-ICE trial, which studied sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression, showed a relative risk reduction in hospitalisation or death at day 29 by 85% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021a). The final analysis of this study has shown a relative risk reduction in hospitalisation or death at day 29 by 79% in patients treated with sotrovimab compared with placebo (Gupta et al, 2021b)

Marketing authorisation

Sotrovimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for the treatment of symptomatic adults, and adolescents (aged 12 years and over and weighing at least 40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. Access to sotrovimab in Northern Ireland for the above indication is

¹ Risk factors for progression to severe disease included the following: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥ 30 kg/m²), immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, and sickle cell disease.

through a Regulation 174 approval or via the European Medicines Agency conditional marketing authorisation.

Eligibility criteria

Patients are eligible to be considered for treatment if the initial criteria below are met:

- Hospitalised for indications other than for the management of acute symptoms of COVID-19²

AND

- SARS-CoV-2 infection is confirmed by either:
 - Polymerase chain reaction (PCR) testing OR
 - Lateral flow test

AND

- [Symptomatic with COVID-19](#) and showing no signs of clinical recovery

AND

- The patient is a member of a 'highest' risk group (as defined in the Department of Health and Social Care commissioned [Independent Advisory Group Report](#))

OR

COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team [MDT] assessment).

Eligible patients may be considered for treatment with one of the following:

- First-line: nirmatrelvir/ritonavir (antiviral)
- Second-line: remdesivir (antiviral)
- Third-line: sotrovimab (nMAB).

Children aged 12-17 years may only be considered for treatment with sotrovimab or remdesivir. For paediatric/adolescent patients (aged 12-17 years inclusive), the eligibility criteria above must be met. Paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment. Additional criteria can be found in the Department of Health and Social Care commissioned [Independent Advisory Group Report](#).

Further information on selecting the most appropriate treatment can be found in the [Clinical Guide which accompanies this policy](#).

Combination treatment with an nMAB and an antiviral is **NOT** routinely recommended.

Patients who have previously received treatment with an nMAB or antiviral, and who meet the eligibility criteria within this policy, may receive treatment under this policy for a subsequent infective episode, if clinically appropriate.

Where patients are ineligible for treatment under this policy, recruitment to the [RECOVERY trial](#), which is studying the use of sotrovimab and oral antivirals in the hospitalised population with COVID-19, should be supported.

First-line: Nirmatrelvir/ritonavir

² This includes patients admitted to community and mental health hospitals. Where possible patients being considered for intravenous treatment should be transferred to a suitable facility for treatment delivery.

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **nirmatrelvir/ritonavir** if:

- Treatment is commenced within 5 days of symptom onset³

AND

- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease (CKD)⁴

AND

- Nirmatrelvir/ritonavir treatment has been deemed safe following guidance from the appropriate specialty team(s) – see the accompanying [Clinical Guide](#) for treatment with antivirals and nMABs.

Second-line: Remdesivir

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **remdesivir** if:

- Treatment with nirmatrelvir/ritonavir is contraindicated or not possible

AND

- Treatment is commenced within 7 days of symptom onset.

Third-line: Sotrovimab

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **sotrovimab** if:

- Clinical judgement deems that an nMAB should be the preferred treatment

OR

- Treatment with remdesivir and nirmatrelvir/ritonavir are both contraindicated or not possible

AND

- Treatment is delivered within 5 days of symptom onset³.

Patients who have received an nMAB within a post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) trial (such as the PROTECT-V trial) who meet the eligibility criteria of this policy can still receive treatment with a sotrovimab, if this is deemed the most appropriate treatment option.

Exclusion criteria

The following patients are **not** eligible for treatment:

- Require hospital-level care for the management of acute COVID-19 illness
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Children aged less than 12 years
- Adolescents (aged 12-17 years) weighing less than 40kg

³ Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (treatment commencement beyond 5 days from symptom onset is off-label).

⁴ Nirmatrelvir/ritonavir may be considered in hospitalised patients with stage 3 CKD. Dose modification is required. See the Summary of Product Characteristics and the section on dosing in the policy for more information.

- Known hypersensitivity reaction to the active substances or to any of the excipients of the products as listed in the respective Summary of Product Characteristics.

The following additional **exclusion criteria** applies to patients being considered for treatment with **nirmatrelvir/ritonavir**:

- Children aged less than 18 years
- Pregnancy
- The patient is taking any of the medications listed as 'do not use' in the [Specialist Pharmacy Service \(SPS\) guidance for nirmatrelvir/ritonavir](#).

The following additional **exclusion criteria** apply if considering for treatment with **remdesivir**:

- Estimated glomerular filtration rate (eGFR) <30 mL/min (except in patients with end-stage renal disease on haemodialysis)
- Alanine transaminase (ALT) $\geq$ 5 times the upper limit of normal.

Remdesivir should be discontinued in patients who develop **any** of the following:

- ALT $\geq$ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

For treatment with remdesivir, an individual clinical decision should be made as to whether pre-treatment urea and electrolytes and liver function tests are required based upon whether recent bloods are available or the patient is considered at risk of undiagnosed liver or kidney disease.

If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as outlined in the UK Clinical Commissioning [Policy](#) for remdesivir in patients hospitalised due to COVID-19.

Dose

The recommended dose of nirmatrelvir/ritonavir is 300mg (two 150mg tablets) nirmatrelvir with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. In patients with moderate renal impairment (CKD stage 3), the dose of nirmatrelvir/ritonavir should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements.

The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3.

The recommended dose of sotrovimab is 500mg to be administered as a single intravenous infusion⁵.

Administration

Nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms³. Clinicians should assure themselves that patients are able to swallow the oral tablets.

Refer to the [Specialist Pharmacy Services guidance](#) and [University of Liverpool COVID-19 Drug Interactions Checker](#) for further information.

⁵ No dose adjustment is recommended in patients with renal or hepatic impairment.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospital-based care due to severe or critical COVID-19 after starting treatment with nirmatrelvir/ritonavir, the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.

Remdesivir

200mg of remdesivir (day 1 loading dose) and 100mg of remdesivir (days 2 and 3 maintenance doses) should be diluted in either a 250ml or 100ml pre-filled bag of 0.9% sodium chloride solution and infused over a minimum of 30 minutes. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days of symptom onset.

Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Sotrovimab

8mls of sotrovimab (62.5mg/ml) should be added to a 100ml pre-filled infusion bag containing 0.9% sodium chloride and administered over 30 minutes. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset³.

Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

Preparation and administration of sotrovimab should be initiated and monitored by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice. Refer to the Specialist Pharmacy Services [institutional readiness document](#) for further information on the handling, reconstitution and administration of the product.

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for [nirmatrelvir/ritonavir](#), [sotrovimab](#) and [remdesivir](#) for special warnings and precautions for use.

Nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir has a risk of serious adverse reactions due to interactions with other medicinal products (see the [SPS guidance](#) for a list of these products).

Initiation of nirmatrelvir/ritonavir, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving nirmatrelvir/ritonavir, may increase plasma concentrations of medicinal products metabolised by CYP3A. Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir/ritonavir.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of nirmatrelvir/ritonavir.
- Loss of therapeutic effect of nirmatrelvir/ritonavir and possible development of viral resistance.

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering

nirmatrelvir/ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Patients should be advised of the possible gastro-intestinal side-effects of treatment with nirmatrelvir/ritonavir (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If nirmatrelvir/ritonavir treatment cannot be tolerated, an alternative treatment can be considered within the options and criteria of this policy. Combination treatment should not be provided⁶.

Remdesivir

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated.

Sotrovimab

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated.

If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered.

Genotyping and sequencing of samples

Sequencing is an important part of surveillance activities to monitor for the development of new variants and drug resistance. Therefore, in patients being considered for treatment with antivirals or nMABs, samples pre-treatment and where part of the clinical pathway, post-treatment, should be prioritised for sequencing. Genotype results do not form part of the eligibility criteria for treatment with antivirals or nMABs in this policy and treatment should not be delayed pending these results.

COVID-19 vaccines

nMABs are not intended to be used as a substitute for vaccination against COVID-19.

Concomitant administration of an nMAB with COVID-19 vaccines has not been studied. Refer to local/national guidelines for vaccine administration and guidance on the risks associated with administration of a SARS-CoV-2 vaccine.

Further information on the timing of COVID-19 vaccination following administration of nMABs is available at the following sites:

- [Liverpool COVID-19 Interactions \(covid19-druginteractions.org\)](https://covid19-druginteractions.org/)
- [Interactions information for COVID-19 vaccines – SPS – Specialist Pharmacy Services](#)

⁶ Unless as part of a formal clinical trial

Pregnancy and women of childbearing potential

Clinicians should refer to the SmPCs for the relevant products for further information on use in pregnancy and women of childbearing potential. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 (available 9:00am to 5:00pm, Monday to Friday, excluding bank holidays) so that they can be followed up. For more information, go to <https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry/>. Clinicians are advised to refer to the SmPC for nirmatrelvir/ritonavir and remdesivir for more information on use during pregnancy or lactation.

Nirmatrelvir/ritonavir

There are no human data on the use of nirmatrelvir/ritonavir during pregnancy to inform the drug-associated risk of adverse developmental outcomes, women of childbearing potential should avoid becoming pregnant during treatment with nirmatrelvir/ritonavir. Nirmatrelvir/ritonavir is **not recommended** during pregnancy and in women of childbearing potential not using effective contraception.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping nirmatrelvir/ritonavir.

Remdesivir

There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should be **avoided** in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

Sotrovimab

There are no data from the use of sotrovimab in pregnant women. The SmPC for sotrovimab states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.

Co-administration

Please see the [SPS guidance](#) for potential interactions involving nirmatrelvir/ritonavir.

There is no interaction expected between nMABs or remdesivir with the drugs listed below. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (<https://www.covid19-druginteractions.org/checker>).

Corticosteroids

The UK CAS Alert on the use of corticosteroids in patients with COVID-19 can be found [here](#). Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Please refer to the [recommendation](#) on the use of corticosteroids in the National Institute for Health and Care Excellence (NICE) Rapid Guideline on Managing COVID-19⁷. nMABs and antivirals should not be regarded as an alternative to corticosteroids.

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 can be found [here](#).

IL-6 inhibitors

⁷ Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found [here](#).

The Clinical Commissioning Policy for the use of IL-6 inhibitors (tocilizumab or sarilumab) in hospitalised patients with COVID-19 who require supplemental oxygen can be found [here](#).

Safety reporting

Any suspected adverse reactions from treatment with the drugs in this policy should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: <https://coronavirus-yellowcard.mhra.gov.uk/>.

Governance

Off-label use of medication

Any provider organisation treating patients with off-label products will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Clinicians are also required to ensure that any data collection requirements are met for the purpose of ongoing surveillance, audit and relevant evaluation, including of clinical effectiveness, around the use of nMABs (see 'Surveillance and service evaluation' section below).

Effective from

This policy will be in effect from the 13 June 2022.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of nirmatrelvir/ritonavir, remdesivir or sotrovimab for COVID-19 would supersede this policy when completed.

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of nMABs and antivirals in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB and antiviral treatment; the impact of nMAB and antiviral treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB and antiviral use, such as generation of new mutations and/or new variants.

Treating clinicians are asked to ensure that all PCR tests undertaken as part of routine clinical care should do this through the hospital laboratory where these samples should be retained for sequencing. Please note that during times of high prevalence, labs will prioritise sending samples from clinical priority groups only. To aid with this, clinicians should ensure PCR samples from clinical priority groups are clearly labelled as such. Further serial sampling for specific patient groups may be requested as part of UKHSA genomic surveillance purposes, or country specific programmes.

Clinicians must ensure that any additional data collection requirements are met for the purpose of relevant surveillance, audit and evaluation around the use of nMABs and antivirals. It is expected that there will be ongoing monitoring (involving sample collection) of selected patients treated with nMABs and antivirals (led by UKHSA, for instance around the potential generation of new variants), as well as academic research to generate new knowledge around clinical effectiveness and other relevant aspects of public health.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
Neutralising monoclonal antibody	Synthetic antibodies that bind to a virus and inhibit its ability to infect host cells and replicate
Spike protein	The part of the SARS-CoV-2 virus that binds to the host cell, which then facilitates its entry into the cell

References

1. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients [published online ahead of print, 2021 Dec 22]. *N Engl J Med*. 2021;10.1056/NEJMoa2116846. doi:10.1056/NEJMoa2116846
2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab [published online ahead of print, 2021 Oct 27]. *N Engl J Med*. 2021;10.1056/NEJMoa2107934. doi:10.1056/NEJMoa2107934
3. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of the Neutralizing SARS-CoV-2 Antibody Sotrovimab in Preventing Progression of COVID-19: A Randomized Clinical Trial. Preprint available at: <https://www.medrxiv.org/content/10.1101/2021.11.03.21265533v1>
4. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19 [published online ahead of print, 2022 Feb 16]. *N Engl J Med*. 2022;10.1056/NEJMoa2118542. doi:10.1056/NEJMoa2118542
5. Hoffmann M, Kruger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralisation – implications for control of the COVID-19 pandemic. Preprint available at: <https://www.biorxiv.org/content/10.1101/2021.12.12.472286v1>