Title: A phase III randomised, multicentric clinical trial evaluating the efficacy of antiviral medication in patients with COVID-19 presenting to primary care: the DAWN Antivirals trial.

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Introduction

The SARS-CoV-2 virus arrived in Belgium in March 2020 marking the start of an epidemic that, by June 1st, 2021, would account for 1,062,001 confirmed cases, 74,149 hospital admissions, and 24,955 fatalities(1). Compared to other European countries, Belgium was hit particularly hard by the first and second waves(2). Similarly to other countries, mortality and morbidity were especially high in older age groups (65 years and older), accounting for over 90% of all COVID-19-related deaths from March 2020 to February 2021(3). The Alpha variant started circulating at the end of 2020, whereas the next two variants, Beta and Gamma, followed in early 2021. The last two variants, Delta and Omicron, took off in May 2021 and November 2021, respectively. The national vaccination campaign was started on 28 December 2020. All Belgian residents were invited for vaccination by age, resulting in 30% full vaccination rates (at least 2 doses) by 20 June 2021(1).

Earlier in the pandemic, COVID treatments mostly focused on hospitalised patients suffering from serious COVID-19 infections. As a result, the COVID-19 research landscape consisted of an overwhelmingly large number of hospital-based clinical trials with only a few trials focusing on outpatient treatments.

In this clinical study report, we report the results of the DAWN Antivirals trial, which was a phase III, prospective, placebo-controlled, individually 1:1:1 randomised, multicentric national clinical trial aimed to evaluate antiviral medication's efficacy against COVID-19 in primary care (clinical trials ID NCT04730206). The study concept was discussed during an ad hoc working group on COVID-19 trials that included infectiologists, general practitioners, and representatives from academic trial units, KCE, Sciensano, the FAGG, the cabinet of the Minister of Health. KCE Trials is a national governmental trial funding body that funds comparative effectiveness trials as well as large repurposing trials. The aim here was to find a repurposing drug that would be suitable for widespread use in COVID-19 patients treated in primary care. The study was subsequently funded by KCE Trials (KCE ID COV20-1279) under a rolling call for academic COVID-19 clinical trials and sponsored by the KU Leuven in collaboration with four research groups from other universities across Belgium. Preparations for the study started in the third quarter of 2020, and the study opened for recruitment in the second quarter of 2021. The trial was prematurely halted in July 2022 due to a slow recruitment rate.

Objectives

The objectives of the DAWN Antivirals trial were to evaluate the efficacy of camostat and later molnupiravir in moderately ill COVID-19 patients presenting to primary care.

Investigational plan

Overall study design

The DAWN Antivirals trial was a prospective, placebo-controlled randomized trial of antiviral therapy in moderately ill COVID-19 patients presenting to primary care. Antiviral medication included camostat (June 2021-July 2022) and molnupiravir (April 2022-July 2022).

The initial aim was to evaluate the effect of antiviral medication on hospitalisation or death within 30 days after randomisation. In April 2021, a second primary endpoint was added, namely the time to first self-reported recovery within 30 days after randomisation. In March 2022, the composite endpoint hospitalisation or death was downgraded to a secondary endpoint and time to first self-reported recovery was the only primary endpoint from then onwards.

The changes in endpoint were in response to the high vaccination rates by mid-2021, leading to lower hospitalisation and mortality rates. Consequently, a dramatic increase in sample size would have been needed, which was beyond the means of the DAWN antivirals trial budget and team. Initially, the sample size was 1316 patients (653 in each treatment arm), to be accrued over 15 months. Randomisation was stratified by age (at least 65 years old versus younger) and comorbidities (at least 3 comorbidities or more versus less than 3). In March 2022, due to a change in endpoints and the addition of a second antiviral drug, the sample size was reduced to 463 patients (150 per arm, plus the patients already recruited prior to this amendment).

Permission for the DAWN Antivirals trial was granted by the ethics committee AZ Delta (ref no. 2020-005911-27/SM006).

The DAWN Antivirals trial involved 5 study visits: one at inclusion, a telephone visit on day 2 and day 4, a home visit on day 8 and a final visit on day 30. Participants were asked to keep a diary for 30 days. Study visits were conducted by the study nurses and involved two home visits. Follow-up information (up until 30 days after randomization) was requested from participants' regular GP. Patients were requested to record the number of pills they took each day in order to monitor treatment compliance. *Figure 1* presents a schematic overview of all trial related procedures.

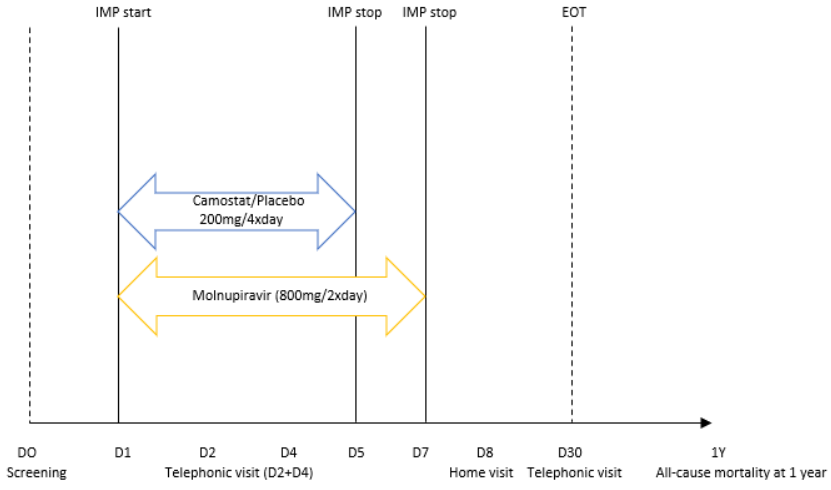


Figure 1: Trial-related procedures

Discussion of study design

Selection of study population

At the start of the study, community-dwelling adults aged at least 50 years old, presenting to primary care with COVID-19 suggestive symptoms for a maximum of 5 days and a positive test for COVID-19 were eligible for the trial. In May 2021, the age cut-off was lowered to 40 years of age to increase the number of eligible patients.

Inclusion criteria

- Aged 40 years or older
- At least 2 suggestive COVID-19 suggestive symptoms at the time of inclusion, with onset of a maximum of 5 days prior to enrolment and which cannot be explained by an alternative cause, and defined by the current official public health authority (Sciensano) case definition
- Positive result on a PCR test or rapid Ag test in the 7 days before inclusion or at the time of inclusion
- Patient is community dwelling
- Participant or their proxy is willing and able to give informed consent for participation in the trial
- Participant is willing to comply with all trial procedures

Exclusion criteria

- Hospital admission is required at the time of possible recruitment
- Positive PCR or rapid antigen test for SARS-CoV-2 in the last 2 months other than in the 7 days prior to recruitment
- Participating in any other interventional drug clinical study at the time of enrolment in the study
- Breastfeeding
- Known seizures in the last 12 months
- Known allergy to camostat or molnupiravir
- Previous adverse reaction to, or currently taking, camostat or molnupiravir
- Patients in palliative care
- Pregnant women or women of childbearing potential who may become pregnant during the trial
- Judgement of the recruiting clinician deems participant ineligible

Removal of patients from therapy or assessment

None

Treatments

Initially, the study only evaluated camostat, at a daily dose of 800mg (200mg four times a day), for seven days. Camostat is a synthetic trypsin-like serine protease inhibitor which blocks the TMPRSS receptor used by the coronavirus to enter the host cells(4). Camostat was selected for this trial based on this in vitro effect and its excellent safety profile(5). Camostat was approved in Japan in 1985 for the treatment of chronic pancreatitis and alkaline esophagitis, but does not have market authorisation in Europe.

In March 2022, a second antiviral drug, molnupiravir, was added to the DAWN Antivirals trial. Molnupiravir is an oral prodrug that has shown antiviral activity against SARS-COV-2. It received a

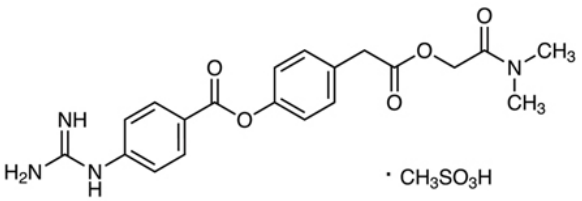
positive advice from the European Medicines Agency (EMA) in November 2021(6) allowing its use in the European Union awaiting marketing authorisation. The Belgian government purchased an amount of molnupiravir for use in Belgian patients but the National Task Force for COVID-19 Therapeutics advised it should be evaluated in a vaccinated population first. The decision to add molnupiravir to the DAWN Antivirals trial at the direct request from the National Task Force was taken in January 2022 and took effect by March 2022. The molnupiravir tablets were commercially manufactured and therefore identifiable by the MSD logo, making the molnupiravir evaluation unblinded.

Treatments administered

Camostat, molnupiravir or placebo

Identity of investigational product

Camostat

Non-proprietary name:	Camostat mesylate
Abbreviated name:	Camostat
Brand name:	FOIPAN®
Chemical name (IUPAC):	Dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy) phenylacetate monomethanesulfonate
Development code:	FOY-305
Molecular formula:	C20H22N4O5 · CH4O3S
Molecular weight:	494.52
Structural formula:	
Description:	Camostat mesylate occurs as white crystals or a crystalline powder. It is sparingly soluble in water, slightly soluble in ethanol (95) and practically insoluble in acetone, chloroform and diethyl ether.
Melting point:	194-198°C

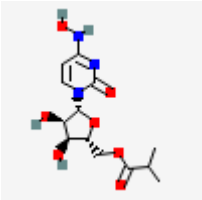
Molnupiravir

Non-proprietary name:	Molnupiravir
Abbreviated name:	Molnupiravir
Brand name:	Lagevrio®
Chemical name (IUPAC):	[(2R,3S,4R,5R)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl]methyl 2-methylpropanoate
Development code:	EIDD 2801

Molecular formula: C13H19N3O7

Molecular weight: 329.31 g/mol

Structural formula:



Description: Molnupiravir is a nucleoside analogue that is N(4)-hydroxycytidine in which the 5'-hydroxy group is replaced by a (2-methylpropanoyl)oxy group. It is the prodrug of the active antiviral ribonucleoside analog N(4)-hydroxycytidine (EIDD-1931), has activity against a number of RNA viruses including SARS-CoV-2, MERS-CoV, and seasonal and pandemic influenza viruses. It is currently in phase III trials for the treatment of patients with COVID-19. It has a role as a prodrug, an anticoronaviral agent and an antiviral drug. It is a nucleoside analogue, an isopropyl ester and a ketoxime. It is functionally related to a N(4)-hydroxycytidine.

Melting point: 156 - 159°C

Method of assigning patients to treatment groups

Eligible participants were randomly assigned using a fully validated and compliant web-based randomisation system. Treatment allocation was 1:1:1 to camostat, molnupiravir and placebo respectively. Randomisation was stratified by age (at least 65 years of age versus younger) and comorbidities (at least 3 comorbidities or more versus fewer than 3) as listed in Table 1.

Table 1: Comorbidities used in the stratification

Comorbidities			
Diabetes type I	Yes/No	Obesity (BMI≥30)	Yes/No
Diabetes type II	Yes/No	Cancer (current)	Yes/No
Hypertension	Yes/No	Solid organ transplant	Yes/No
Heart conditions (including heart failure, coronary artery disease or cardiomyopathies)	Yes/No	Neurological condition (including dementia)	Yes/No
Asthma (current; moderate to severe)	Yes/No	Thalassaemia	Yes/No
COPD	Yes/No	Sickle cell disease	Yes/No
Cystic fibrosis	Yes/No	Renal function impairment	Yes/No
Pulmonary fibrosis	Yes/No	Liver function impairment	Yes/No

Selection of doses in the study

For camostat: The dosage for treating acute symptoms of chronic pancreatitis is 3x200 mg per day, and for postoperative reflux oesophagitis is 3x100 mg per day. Camostat significantly reduced SARS-CoV-2 viral entry in a lung-derived human cell line (Calu-3) with an EC50 of 87 nM of camostat (EC50

= half maximal effective concentration) and no interference in cell viability reported.(7) Additional studies report camostat and its active metabolite FOY251 directly inhibit TMPRSS2 at IC50 of 6nM for camostat and IC50 of 33nM for FOY-251.(8) Another group reported similar findings: IC50 values were 4nM (camostat mesylate) and 70nM (FOY251).(4) Titration experiments with VSV pseudotypes and Calu-3 lung cells as targets revealed that entry inhibition by FOY-251 was only slightly reduced as compared to camostat mesylate, with EC50 values of 107 nM (camostat mesylate) and 178 nM (FOY-251).(4)

Furthermore, Hoffmann et al report "Guanidinobenzoate-containing drugs such as camostat mesylate and GBPA inhibit TMPRSS2 by first forming a noncovalent precomplex which is then catalysed to form a long-lived covalent complex that is the main source of inhibition."(4) This could compensate for the relatively short plasma half-life of GBPA.

In a model of SARS-CoV-2 infection of pluripotent stem cell derived human lung alveolar type 2 cells, the addition of camostat successfully blocked downstream activities seen after SARS-CoV-2 infection.(9) Of relevance, data on the distribution of camostat in rat and dog revealed camostat in the lung to be 1- to 3.8-fold that in the plasma.(10) As a result, the target concentration for COVID-19 patients is 0.1 µM. After a dose of 200 mg, GBPA (the active metabolite of camostat) in humans is sufficient to achieve plasma concentrations in this range. The reported PK parameters for a 200 mg oral dose of camostat (2 x 100 mg tablets) are: maximum plasma concentration of GBPA (Cmax) 87 ng/mL; time to maximum concentration (Tmax) 40 min; area under the plasma concentration time curve (AUC) 10,400 ng.min/mL; terminal half-life (T1/2) 100 min. The GBPA Cmax corresponds to a concentration of 87/409.4=213nM. With a 4x200 mg dosage and dosing regimen, the camostat plasma concentration is maintained above the 0.1 µM target range for a longer period of time (10.4 hours/day as compared to 9.6 hours/day for 3x300 mg dosed), resulting in greater exposure to the drug.

For molnupiravir: The dosage as accepted by EMA is 4 capsules of 200 mg, taken twice daily for 5 days (total daily dose of 1600 mg)

Blinding

The placebo tablets were manufactured by the same manufacturer as camostat, identical in size and appearance to the camostat tablets. Patients and treating physicians were thus blinded for the camostat versus placebo comparison; patients and treating physicians were unblinded for the molnupiravir versus placebo comparison as the molnupiravir tablets did not match the placebo tablets. The outcome assessor was blinded for all comparisons (except for the patient reported outcomes in case of molnupiravir).

For emergency unblinding, the randomisation list could be accessed remotely through a digital platform, which was available 24/7. Unblinding would be done by a dedicated member of the study team who was otherwise not involved in the safety reporting or data management.

The rest of the study team and principal investigators (PIs) remained blinded to emerging results throughout the trial. During the course of the trial, only those on the independent Data Monitoring Committee (iDMC) had access to the unblinded interim results. Those ascertaining the outcome and managing the data were equally blinded to participant allocation.

Prior and concomitant therapy

We expected any concomitant medication to be mainly symptomatic. As a result, routinely used medications for the alleviation/treatment of symptoms of COVID-19 were permitted. Nevertheless, we recorded symptom-controlling concomitant medication and had planned to account for these in the analyses.

Should other anti-viral therapies to treat SARS-CoV-2 have become approved and implemented in routine clinical practice, these would also have been permitted. Other experimental therapies were not permitted.

Any other medication that the participant was receiving at the time of randomisation or during 30 days after randomisation was recorded in the patient diary supplemented by follow-up data from the participant's regular GP, along with:

- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

Treatment compliance

Compliance was monitored via the recordings in the participants' diary. Participants were asked to record each tablet that was taken for the entire duration of the treatment. All medication was collected at the end of treatment by the study nurses and brought to the regional PI.

Drug accountability was performed according to the relevant Good Clinical Practice (GCP) guidance. The manufacturer shipped camostat and the matching placebo to a European depot in Belgium which was responsible for checking the shipment and securely storing the Investigational Medicinal Product (IMP). Molnupiravir was also transported to and stored at this European depot.

Trial medication was shipped from the European depot to the participant's home using a specialized courier, under the supervision of the PI. The participant's name and address were only made available to the courier by the PI or delegated staff, the sponsor and depot were only aware of the subject ID and kit number. Upon delivery, the participant was asked to record the kit number in their patient diary.

At the 8-day home visit by the study nurse, IMP was collected and returned to the regional PI. The study nurse checked the remaining tablets or capsules against what was noted by the participant in the diary and asked for clarification from the participant if needed. In addition, the study nurse checked compliance with study medication at the day 2 and day 4 telephone/video calls, to supplement information on IMP use should the diary not be completed fully by the participant In the eCRF, the following was recorded: number of remaining tablets or capsules, whether or not this corresponds with the diary and if not, the reason for this. Any discordance between diary entries and remaining IMP was recorded but diary entries will be left unchanged. At the end of the study, the European depot collected all IMP from the regional PIs for destruction. Adequate records of the study receipts of IMP, disposition of IMP, returns of (un)used supplies and its destruction were kept by the regional PIs and the European depot. Records of actual administration of IMP will be kept in the diary by the participants.

Efficacy and safety variables

Efficacy and safety measurements assessed

Primary endpoint: time to first self-reported recovery within 30 days after randomisation.

Secondary endpoints

- All-cause unplanned hospital admission for at least 24 hours or all-cause mortality within 30 days after randomisation;
- Time to sustained recovery within 14 days = time from randomisation to self-reported recovery within 14 days and remaining recovered until day 30 after randomisation;
- All-cause unplanned hospital admission for at least 24 hours within 30 days after randomisation;
- All-cause mortality within 30 days after randomisation;
- WHO clinical progression scale at 8 days and 30 days after randomisation

0	Uninfected
1	Ambulatory, asymptomatic
2	Ambulatory, symptomatic independent
3	Ambulatory, symptomatic, assistance needed
4	Hospitalized, no oxygen therapy
5	Hospitalized, oxygen by mask or nasal prongs
6	Hospitalized, oxygen by NIV or high flow
7	Hospitalized, intubation and mechanical ventilation pO2/FiO2 ≥150 or SpO2/FiO2 ≥200
8	Hospitalized, mechanical ventilation pO2/FiO2 <150 or vasopressors
9	Hospitalized, mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis or ECMO
10	Dead

- At least once oxygen administration over a period of 30 days after randomisation;
- At least once ventilated over a period of 30 days after randomisation;
- Admission to ICU over a period of 30 days after randomisation;
- All-cause mortality at 1 year after randomisation;
- Cardiovascular and thromboembolic complications within 7 days and 30 days after randomisation;
- Symptom duration for each individual symptom over a period of 30 days after randomisation;
- Duration of hospital admission for those admitted to hospital over a period of 30 days after randomisation;
- Number of contacts with health services including general practitioners, out-of-hours services, emergency department visits, specialist assessments over a period of 30 days after randomisation;
- Number of hospital assessments without admission over a period of 30 days after randomisation;
- Consumption of antibiotics over a period of 30 days after randomisation, expressed in defined daily dose;
- Quality of life as measured by the EQ-5D-5L at 7 days and 30 days after randomisation.

Drug concentration measurements

Not applicable

Data quality assurance

Data quality was assured through independent monitoring by monitors from KU Leuven/UZ Leuven. The first monitoring visit at each site was conducted within 8 weeks after inclusion of the first two study subjects at that site. At least one on-site monitoring visit was to be completed at each site having enrolled at least 2 patients. Priority was given to high recruiting sites.

A total of 25% of expected study subjects would have been monitored, and 100% of source data verification would be performed for the first 2 randomized study subject at each site. The remaining randomized subjects were randomly selected for review of critical data only.

Monitoring activities and frequency were intended to be balanced across all participating regions in order to provide timely feedback to the regional study nurses and to identify opportunities for (re-) training where needed.

Critical data were defined as follows:

- Documentation for obtaining informed consent in the subject's source records
- Subject eligibility (in- and exclusion criteria)
- Randomisation of subjects per protocol (as applicable) & documentation thereof
- Safety assessments (including evaluation of severity, causality, seriousness and action taken,…)
- Documentation & reporting of serious adverse events (SAEs) and other reportable safety events, as defined in the protocol
- Parameters determining primary endpoint(s), as defined in the protocol
- Parameters determining secondary endpoint(s), as defined in the protocol
- Patient diaries

For at least 25% of subjects monitored (see above), the Monitor reviewed drug accountability and documentation related to the IMP kits returned to the site of the regional PI, prior to approving the return of used IMP kits to the depot for destruction.

For the above referenced critical data, the Monitor verified protocol compliance and cross-verified the accuracy, completeness and integrity of collected study data in the source documents, (e)CRF and other study-related records, and any changes thereto in accordance with GCP and ALCOAC (Attributable, Legible, Complete, Original, Accurate and Contemporaneously) principles.

The Monitor reviewed all Informed Consent Forms (ICF) and subject logs (as applicable) and confirmed the existence of all study subjects with the subject's source records.

The Monitor checked the Informed Consent Form for each subject to ensure that:

- The process for obtaining and documenting informed consent for each subject is adequate. The current EC approved version of the ICF has been used
- Informed consent (IC) has been obtained prior to performing any study-specific procedures
- The procedure for obtaining IC is documented in the source documents

The Monitor reviewed that all required essential documents at investigator research sites were available, accurate, complete and filed in the relevant sections of the study files.

For this study, the Project Manager appointed by the Sponsor was responsible for maintaining the Trial Master File (TMF) throughout the lifetime of the study. The Monitor reviewed the TMF only once at the Sponsor location, as part of study close-out activities.

Statistical methods planned in the protocol and determination of sample size

Statistical and analytical plans

The primary analysis for each antiviral was a time to event analysis considering mortality as a competing risk. The event rates for the antiviral and placebo group would be estimated using cumulative incidence functions (CIF), the resulting CIF curves would be compared using a stratified Gray's test. The treatment effect would be estimated by the subdistribution hazard ratio obtained

using a Fine&Gray regression model. The model would include a factor for randomised treatment. The baseline hazard would be stratified by the stratification factors age and number of comorbidities.

Determination of sample size

This was a group sequential trial with one interim analysis at which could be stopped for early efficacy or futility. We assumed median time to recovery of 6 days in the study population, with an intervention lowering the median time to recovery to 4 days.

The sample size for time to first self-reported recovery, has been calculated using this difference of at least two days in median recovery time. Assuming such a difference, an exponential distribution for time to recovery with a median of 6 days for the placebo group, and 15% dropout of which 10% occurs uniformly up to day 8 and the remaining 5% up to day 30, we would require 263 events in total to achieve 90% power at a two-sided alpha of 0.05 using using a stratified Gray's test. This corresponds with a subdistribution hazard ratio of 1.5.

Under these assumptions, we would randomize 450 patients to an antiviral or eligible placebo for this antiviral. Patients already randomised before the addition of the third arm will contribute to the camostat vs placebo comparison only. Given this number is limited and to simplify the switch to a 1:1:1 randomization, the total sample size for this comparison may be slightly higher as these patients will be added to the camostat vs placebo comparison.

For both antiviral, one interim analysis was planned. Both interim analyses would be performed simultaneously when 132 events had been reached for both analyses, i.e. in the respective antiviral group and associated control-group together. It might be that at this time point already more than 132 events were recorded for one antiviral group and its associated control-group together. The stopping boundaries for both futility and efficacy are based on the O'Brien Fleming spending function from Lan-DeMets.

The sample size calculation was performed with EAST version 6.5.

Changes in the conduct of the study or planned analyses

The following changes have been made over the course of the study:

Amendment #	Date	Reason for amendment
1	28/04/2021	To lower the age of patients eligible for the trial from 50 years or older to 40 years or older To add a co-primary endpoint of first self-reported recovery, and add additional secondary endpoints To change the end of SAE follow-up To lower the age used in the randomisation stratification from 75 years to 65 years
2	16/06/2021	To change the time period of the exclusion criterion of positive PCR or rapid tests
3	12/10/2021	To allow a positive PCR or rapid test in the 7 days before inclusion or at the time of inclusion (instead of the required rapid test at the time of inclusion) To add a requirement for at least 2 symptoms of COVID-19 at time of inclusion

		To allow for the investigator to perform the informed consent procedure via video call. To delete information regarding the patient app.
4	07/02/2022	To add molnupiravir as a third arm To change the primary endpoint to recovery only and list hospitalisation or death as a secondary endpoint To adapt the sample size to this change in endpoints

Given the trial was terminated early, the statistical analysis plan was adapted before data base lock to perform only descriptive analyses.

Study patients

Disposition of patients

The trial was prematurely terminated on 12 July 2022 because of insufficient recruitment. As a result, only descriptive analyses were performed.

In total, 44 participants were recruited in the DAWN Antivirals trial between June 2021 and July 2022; 19 were randomized to camostat, 8 to molnupiravir and 17 to placebo.

There were no deaths in the trial. There was one participant lost to follow-up before day 30. The reason for the drop out is unknown as no further contact was made despite multiple attempts.

Protocol deviations

All patients met the inclusion and exclusion criteria. Since the study was terminated early, other protocol deviations are not reported.

Efficacy evaluation

Demographic and other baseline characteristics

The demographic and other baseline characteristics for the 44 included participants are listed in the table below.

Table 2: Demographic and other baseline characteristics

	Camostat (n=19)	Molnupiravir (n=8)	Placebo (n=17)
Male gender (n)	9	6	9
Mean age (years)	61	61	60
Pregnancy (n)	0	0	0
Diabetes type I (n)	1	1	1
Diabetes type II (n)	2	2	1
Hypertension (n)	8	3	6
Heart conditions (n)	4	1	1
Asthma (n)	2	2	1
COPD (n)	0	0	0
Cystic fibrosis (n)	0	0	0
Pulmonary fibrosis (n)	0	0	0
Obesity (n)	5	3	4
Cancer (n)	0	0	1
Solid Organ Transplant (n)	0	0	0
Neurological (n)	0	0	0
Thalassaemia (n)	0	0	0

Sickle Cell (n)	0	0	0
Renal function impairment (n)	0	0	1
Liver function impairment (n)	1	0	0
Mean temperature at recruitment (°C)	36.49	36.84	36.46
Mean breathing rate (per minute)	15.8	17.0	14.4
Mean oxygen saturation (%)	97.3	97.1	97.7
Dyspnoea (n)	1	1	1
Tachycardia (≥100 bpm; n)	1	0	2
Confusion (n)	0	0	0
Anosmia or ageusia (n)	0	2	1
Vaccinated, fully with booster (n)	15	8	14
Vaccinated, fully without booster (n)	4	0	2
Partially vaccinated (n)	0	0	1

Measurement of treatment compliance

Participants randomised to camostat or placebo were required to take 56 tablets in total (4*2 tablets per day for 7 days) whereas participants randomised to molnupiravir were required to take 40 tablets in total (2*4 tablets per day for 5 days). The median number of tablets taken by participants randomised to camostat was 54, to placebo it was 54, to molnupiravir it was 40. Total number of tablets taken is listed in Table 2 below.

Table 3: Number of tablets taken by participants

Number of tablets taken as per diary	Camostat 56 tablets, n=19	Molnupiravir 40 tablets, n=9	Placebo 56 tablets, n=17
12	1		0
26	0		1
40		8	
44	1		0
46	0		1
50	0		2
52	6		3
54	5		8
56	6		2
Missing data		1	

Efficacy results

Analysis of efficacy

The median number of days until self-reported recovery within 30 days after randomisation was 7.5 (95% CI 5-11) in the camostat group, 23.5 (95% CI 2-undefined) in the molnupiravir group, and 10 (95% CI 5-19) in the placebo group. On day 8, 11/19 of participants in the camostat group, 6/8 of participants in the molnupiravir group and 12/16 participants in the placebo group were still symptomatic according to the WHO clinical progression scale. On day 30, this had decreased to 4/19 of participants in the camostat group, 4/7 of the molnupiravir group and 5/16 of the placebo group.

Statistical/analytical issues

Adjustments for covariates

Since the trial was terminated early, no correction for covariates was performed.

Handling of dropouts or missing data

Since the trial was terminated early, no imputations were performed.

Interim analyses and data monitoring

The independent Data Monitoring Committee (iDMC) has convened once, for the evaluation of safety data. No serious adverse events were reported and the iDMC committee recommended no changes. No interim analysis has been performed.

Multicentre studies

Given the limited number of patients, no by-centre analysis was performed.

Multiple comparisons/multiplicity

Each comparison of an antiviral with placebo would be done at a two-sided significance level of 0.05.

Since only 1 primary endpoint was defined, no adjustment of the significance level would have been required.

For secondary efficacy endpoints, due to the exploratory nature of the efficacy analyses, no adjustment for multiple comparisons would be made.
However, since the trial was premature terminated, only descriptive analyses were performed.

Use of an efficacy subset of patients

Subgroup analyses would have been performed for the primary endpoint only in the Full Analysis Set.

The following subgroups were of interest:

1. Duration of symptoms before start of treatment (at least 3 days or less)
2. Body temperature at baseline (at least 38°C or less)
3. Age (above 65 years or less)
4. Number of co-morbidities (at least 3 or less)

Appropriate summary statistics based on the multiply imputed data per treatment and estimated treatment differences would be presented for each subgroup. In addition, the interaction between the above subgroups and randomized treatment would be tested to assess whether the treatment effect differs according to subgroup. The treatment difference per subgroup would be estimated from a logistic regression model that includes a factor for the stratification factors age and number of co-morbidities (if different from the subgroup), treatment, subgroup and their interaction.

However, since the trial was premature terminated, no subgroup analyses were performed.

Active control studies intended to show equivalence

Not applicable

Examination of subgroups

Not applicable

Tabulation of individual response data

Not applicable

Drug dose, drug concentration, and relationships to response

Not applicable

Drug-drug and drug-disease interactions

Not applicable

By-patient displays

Not applicable

Safety evaluation

Adverse events

Brief summary of adverse events

During follow-up until 30 days after randomisation, there were no cardiovascular or thromboembolic complications, no hospital admissions and no deaths in either group. Two participants in the camostat group and one participant in the placebo group reported a hospital visit without admission. Two participants (both in the camostat group) used antibiotics.

There were no serious adverse events in either group. There were 51 non-serious adverse events in 13 participants in the camostat group, 84 adverse events in 8 participants in the molnupiravir group and 98 adverse events in 14 participants in the placebo group. The five most common adverse events were fatigue (n=20), cough (n=12), constipation (n=10), nasopharyngitis (n=10), and diarrhoea (n=9).

Display of adverse events

Table 4: All adverse events

		Placebo (n=17)	Camostat (n=19)	Molnupiravir (n=8)
Number of Events	n	98	51	84
Number of subjects with Adverse Events	n (%)	14 (82.35%)	13 (68.42%)	8 (100.00%)
GASTROINTESTINAL DISORDERS	n/N (%)	10 (58.82%)	5 (26.32%)	3 (37.50%)
Constipation	n/N (%)	4 (23.53%)	4 (21.05%)	2 (25.00%)
Diarrhoea	n/N (%)	6 (35.29%)	1 (5.26%)	2 (25.00%)
Vomiting	n/N (%)	2 (11.76%)	1 (5.26%)	1 (12.50%)
Abdominal pain	n/N (%)	2 (11.76%)	0 (0.00%)	1 (12.50%)
Nausea	n/N (%)	1 (5.88%)	1 (5.26%)	0 (0.00%)
Abdominal pain upper	n/N (%)	1 (5.88%)	0 (0.00%)	1 (12.50%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n/N (%)	6 (35.29%)	9 (47.37%)	5 (62.50%)
Fatigue	n/N (%)	6 (35.29%)	9 (47.37%)	5 (62.50%)
Chills	n/N (%)	1 (5.88%)	2 (10.53%)	2 (25.00%)
Pyrexia	n/N (%)	0 (0.00%)	1 (5.26%)	0 (0.00%)
NERVOUS SYSTEM DISORDERS	n/N (%)	8 (47.06%)	4 (21.05%)	3 (37.50%)
Headache	n/N (%)	4 (23.53%)	2 (10.53%)	2 (25.00%)
Anosmia	n/N (%)	4 (23.53%)	0 (0.00%)	1 (12.50%)
Dizziness	n/N (%)	1 (5.88%)	3 (15.79%)	3 (37.50%)
Ageusia	n/N (%)	2 (11.76%)	0 (0.00%)	2 (25.00%)
Dysgeusia	n/N (%)	1 (5.88%)	0 (0.00%)	0 (0.00%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n/N (%)	5 (29.41%)	5 (26.32%)	6 (75.00%)
Cough	n/N (%)	4 (23.53%)	3 (15.79%)	5 (62.50%)
Oropharyngeal pain	n/N (%)	2 (11.76%)	3 (15.79%)	3 (37.50%)
Coughing	n/N (%)	0 (0.00%)	1 (5.26%)	0 (0.00%)
Dyspnoea	n/N (%)	1 (5.88%)	0 (0.00%)	1 (12.50%)
INFECTIONS AND INFESTATIONS	n/N (%)	5 (29.41%)	2 (10.53%)	3 (37.50%)
Nasopharyngitis	n/N (%)	5 (29.41%)	2 (10.53%)	3 (37.50%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n/N (%)	4 (23.53%)	3 (15.79%)	4 (50.00%)
Myalgia	n/N (%)	3 (17.65%)	1 (5.26%)	4 (50.00%)

Arthralgia	n/N (%)	1 (5.88%)	1 (5.26%)	0 (0.00%)
Back pain	n/N (%)	0 (0.00%)	1 (5.26%)	0 (0.00%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	n/N (%)	3 (17.65%)	2 (10.53%)	3 (37.50%)
Pruritus	n/N (%)	3 (17.65%)	2 (10.53%)	3 (37.50%)
Rash	n/N (%)	1 (5.88%)	0 (0.00%)	1 (7.69%)
PSYCHIATRIC DISORDERS	n/N (%)	2 (11.76%)	1 (5.26%)	1 (12.50%)
Confusional state	n/N (%)	2 (11.76%)	0 (0.00%)	0 (0.00%)
Emotional distress	n/N (%)	0 (0.00%)	1 (5.26%)	0 (0.00%)
Agitation	n/N (%)	0 (0.00%)	0 (0.00%)	1 (12.50%)
CARDIAC DISORDERS	n/N (%)	1 (5.88%)	0 (0.00%)	1 (12.50%)
Palpitations	n/N (%)	1 (5.88%)	0 (0.00%)	1 (12.50%)
EYE DISORDERS	n/N (%)	0 (0.00%)	1 (5.26%)	0 (0.00%)
Myopia	n/N (%)	0 (0.00%)	1 (5.26%)	0 (0.00%)

Analysis of adverse events

Considering no serious adverse events were reported and the trial was prematurely terminated, no further analysis of adverse events was performed.

Deaths, other serious adverse events, and other significant adverse events

Listing of deaths, other serious adverse events and other significant adverse events

There were no deaths, other serious adverse events and other significant adverse events.

Narratives of deaths, other serious adverse events, and other significant adverse events

Not applicable

Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

Not applicable

Clinical laboratory evaluation

Not applicable

Vital signs, physical findings, and other observations related to safety

Not applicable

Safety conclusions

In this prematurely terminated trial with 44 participants, no serious adverse events were reported. The five most common adverse events were fatigue (n=20), cough (n=12), constipation (n=10), nasopharyngitis (n=10), and diarrhoea (n=9). All of these are also COVID-19 related symptoms, require little to no intervention and are mostly self-limiting.

Discussion and overall conclusions

The DAWN Antivirals trial was introduced during a period when there was still an urgent need for effective treatment of COVID-19 patients in primary care. Recruitment to the trial was however insufficient and the trial was subsequently halted after 13 months.

The trial opened for recruitment in June 2021, when vaccination campaigns were well advanced in Belgium. This led to a lower risk of serious illness from COVID-19 to the population and a decreased interest in participating in a trial for a disease that was no longer considered a major threat. The pandemic itself had a huge impact on the trial: recruitment settings changed from testing centres to general practices to a decentralised system with remote informed consent; general practice was overwhelmed leading to little interest from GPs; study nurses were in short supply and charging very

high rates; the number of potential participants was highly dependent on virus circulation in the population.

Strengths and weaknesses

The DAWN Antivirals trial was the first randomised controlled trial in Belgium with an unregistered product in primary care. For this reason, regulatory authorities were reluctant to give approval for the study and additional checks were requested to safeguard participants which had an impact on the team and budget.

We developed a decentralised model which allows participation from people across Belgium without geographic restrictions. However, such a model is very dependent on awareness of the trial and expensive in terms of study nurse time when home visits are required.

Recommendations for future studies

Conducting trials in a primary care context is challenging, especially during a pandemic. To date, the largest randomised trial investigating the efficacy of novel therapeutic agents against COVID-19 in the community, is the UK-based PANORAMIC trial.(11) This trial of more than 25.000 participants was able to build on previous study experience, including the Principle trial(12) and the ALIC4E trial.(13) In addition, the UK has a strong primary care research infrastructure facilitating the recruitment of participants in busy clinical environments.

Having an established research infrastructure that is able to support primary care services in the delivery of trials, is of the utmost importance. The REMAP-CAP trial(14), which evaluated treatments for COVID-19 in hospitalized patients across Europe, struggled to recruit until it could draw on the PREPARE research infrastructure (https://www.remapcap.org/). Such a research infrastructure should be tailored to the specific needs of primary care, being that it should be present in the practices and staffed by experienced trial personnel. IT services should allow maximum digitalization of data processes. Where possible, remote procedures should be adopted to allow participants from other practices to join the study without limitations. Pre-established research infrastructure may already overcome some of those barriers, and increase expertise in both sponsor and clinical teams. This will require funders to acknowledge that primary care research comes with its own complexities that should be funded appropriately in order to build a sufficiently large sponsor team.

Reference list

1. Sciensano. COVID-19 Epidemiologisch Bulletin Brussels, Belgium2021 [Available from: https://covid-19.sciensano.be/sites/default/files/Covid19/COVID-19_Daily%20report_20210601%20-%20NL.pdf.
2. Ingelbeen B, Peckeu L, Laga M, Hendrix I, Neven I, van der Sande MA, et al. Reducing contacts to stop SARS-CoV-2 transmission during the second pandemic wave in Brussels, Belgium, August to November 2020. Euro Surveill. 2021;26(7).
3. Vandael E, Latour K, Islamaj E, Panis LI, Callies M, Haarhuis F, et al. COVID-19 cases, hospitalizations and deaths in Belgian nursing homes: results of a surveillance conducted between April and December 2020. Arch Public Health. 2022;80(1):45.
4. Hoffmann M, Hofmann-Winkler H, Smith JC, Kruger N, Sorensen LK, Sogaard OS, et al. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. bioRxiv. 2020.

5. Kitagawa J, Arai H, Iida H, Mukai J, Furukawa K, Ohtsu S, et al. A phase I study of high dose camostat mesylate in healthy adults provides a rationale to repurpose the TMPRSS2 inhibitor for the treatment of COVID-19. Clin Transl Sci. 2021;14(5):1967-76.
6. European Medicines Agency. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19 2021 [Available from: https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19.
7. Hoffmann M, Schroeder S, Kleine-Weber H, Muller MA, Drosten C, Pohlmann S. Nafamostat Mesylate Blocks Activation of SARS-CoV-2: New Treatment Option for COVID-19. Antimicrob Agents Chemother. 2020;64(6).
8. Shrimp JH, Kales SC, Sanderson PE, Simeonov A, Shen M, Hall MD. An Enzymatic TMPRSS2 Assay for Assessment of Clinical Candidates and Discovery of Inhibitors as Potential Treatment of COVID-19. bioRxiv. 2020.
9. Huang J, Hume AJ, Abo KM, Werder RB, Villacorta-Martin C, Alysandratos KD, et al. SARS-CoV-2 Infection of Pluripotent Stem Cell-Derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response. Cell Stem Cell. 2020.
10. Midgley I, Hood AJ, Proctor P, Chasseaud LF, Irons SR, Cheng KN, et al. Metabolic fate of 14C-camostat mesylate in man, rat and dog after intravenous administration. Xenobiotica. 1994;24(1):79-92.
11. Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet. 2023;401(10373):281-93.
12. Group PTC. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021;397(10279):1063-74.
13. Butler CC, van der Velden AW, Bongard E, Saville BR, Holmes J, Coenen S, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. Lancet. 2020;395(10217):42-52.
14. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Ann Am Thorac Soc. 2020;17(7):879-91.

Appendices

Study information

Protocol and protocol amendments

List of IECs or IRBs

Members of the iDMC:

- Prof Dr Roger Damoiseaux (University of Utrecht, the Netherlands), chair
- Prof Dr Matthew Thompson (University of Washington, US)
- Prof Dr Malene Plejdrup Hansen (University of Aalborg, Denmark)
- Dr Elisabeth Coart (IDDI), statistician
- Dr Anna Ivanova (KU Leuven, Belgium), non-voting independent statistician

List and description of investigators and other important participants in the study, including brief CVs or equivalent summaries of training and experience

Coordinating investigator Prof Dr Ann Van den Bruel

Signatures of principal or coordinating investigator or sponsor's responsible medical officer

Ann Van den Bruel

Digitally signed by Ann Van den Bruel
Date: 2023.06.22 15:57:17 +02'00'

Listing of patients receiving investigational product from specific batches where more than one batch was used

Not applicable

Audit certificates

Not applicable

Documentation of statistical methods

Not applicable

Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

Not applicable

Publications based on the study

One paper describing the process evaluation of the trial is currently under preparation and will be submitted to a peer-reviewed journal for publication.

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