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Supplementary appendix

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SUPPLEMENTARY APPENDIX

Dipeptidyl Peptidase-1 Inhibition in Patients Hospitalized with COVID-19: a Multicentre Randomized Double-Blind Placebo Controlled Trial

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Full Inclusion criteria

- Male or female
- ≥16 years of age
- SARS-CoV-2 infection (clinically suspected[+] or laboratory confirmed*).
- Admitted to hospital as in-patient less than 96 hours prior to randomisation^
- Illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (e.g. chest x-ray, computed tomography (CT) scan)

      OR
    - Evidence of rales/crackles on physical examination

      OR
    - Peripheral capillary oxygen saturation (SpO2) ≤94% on room air prior to randomization

      OR
    - Requiring supplemental oxygen.

      OR
    - Lymphocyte count <1 x 10^9 cells per litre (L)
- Participant (or legally authorized representative) provides written informed consent
- Able to take oral medication
- Participant (or legally authorised representative) understands and agrees to comply with planned trial procedures.

*Laboratory-confirmed: SARS-CoV-2 infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen < 96 hours prior to randomization.

[+]Clinically suspected: SARS-CoV-2 infection should be suspected when a patient presents with (i) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and (ii) compatible chest X-ray findings (consolidation or ground-glass shadowing); and (iii) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). However, the diagnosis remains a clinical one based on the opinion of the managing doctor

^Where a patient has been admitted to hospital for a non COVID-19 reason and develops COVID-19 symptoms whilst an in-patient, randomisation may occur up to 96 hours from onset of symptoms.

Full Exclusion criteria

- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 5 times the upper limit of normal, result within 72 hours of randomization (the result closest to randomization should be used if several results are available).
- History of severe liver disease
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30), result within 72 hours of randomization (the result closest to randomization should be used if several results are available)
- Absolute neutrophil count less than 1.0 x 10^9 cells per L within 72 hours of randomization (the result closest to randomization should be used if several results are available)
- Current treatments with potent Cyp3A4 inducers/inhibitors (e.g Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin or rifampicin)
- HIV treatments - current treatment with protease/integrase inhibitors or non-nucleoside reverse transcriptase inhibitors*
- Pregnant or breast feeding.
- Anticipated transfer to another hospital which is not a trial site within 24 hours.
- Allergy to Brensocatib
- 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. Co-enrolment with COVID-19 trials is allowed as per co-enrolment agreements and/or individual decision by the CI.

Women of child-bearing potential must be willing to have pregnancy testing prior to trial entry.

Adverse events and adverse events of special interest

Each investigator was responsible for the detection and documentation of events meeting the criteria and definition of an adverse event. Patients were reviewed regularly whilst in hospital and telephone calls performed on days 3, 5, 8, 11, 15 and 29 in patients not in hospital at these time points in order to detect and document adverse events.

Adverse events of special interest (AESIs) were monitored throughout the trial and included hyperkeratosis, dental complications, and infections other than COVID-19,

including serious infections. These AESIs were pre-specified based on the mechanism of action for Brensocatib. Brensocatib inhibits dipeptidyl peptidase 1 (DPP1; cathepsin C) resulting in reduced levels of neutrophil serine proteases. Papillon-Lefèvre Syndrome (PLS) is a rare genetic disorder with complete or near complete absence of DPP1 activity. It is characterized by palmoplantar hyperkeratosis and periodontal disease. Patients with PLS do not appear to be at increased risk of infections but since neutrophil responses to bacterial infections are considered an important part of the immune response and NSPs participate in such responses, observation for bacterial infections is considered an important part of safety assessments with DPP1 inhibitors.

Supplementary results

	Placebo N=214	Brensocatib N=192
Enrolled in RECOVERY	65(30.4)	49(25.5)
Enrolled in REMAP CAP	4(1.9)	5(2.6)
Low-dose Dexamethasone	171(79.9)	155(80.7)
Azithromycin	12(5.6)	4(2.1)
Tocilizumab	7(3.3)	7(3.6)
Aspirin	11 (5.1)	12 (6.3)
Colchicine	8 (3.7)	5 (2.6)
Convalescent plasma	7 (3.3)	8 (4.2)
REGN-COV2	5 (2.3)	3 (1.6)
Remdesivir	51(23.8)	47(24.5)
Antibiotics	133(62.1)	113(58.9)

Table S1. Co-medications and COVID-19 treatments received. *Numbers in cells are n(%)

Subgroup analyses of the primary outcome

The primary endpoint was analysed for the following sub-groups:

- (a) Age <65 years and (b) ≥65 years
- (a) Male and (b) Female
- Clinical status at baseline (a) 3, (b) 4 and (c) 5
- Enrolment in the RECOVERY trial (a) Yes and (b) No
- Symptom duration (days): (a) <10 and (b) ≥10

Age (years): (a) <65 years and (b) ≥ 65

Table S2 shows the subgroup analysis for age. Overall, there was no evidence that the treatment effect was moderated by age group: interaction effect 1.13 (0.47, 2.72); p-value = 0.731.

Table S2: Subgroup analysis for age group

	Placebo	Brensocatib	Age group	Effect size (99% CI)	p value
Less than 65 years					
Not Hospitalized, no limitations on activities	29/121(24.0)	17/104(16.3)	Less than 65 years	0.69(0.42,1.13)	0.050
Not Hospitalized, limitations on activities	78/121(64.5)	73/104(70.2)	65 years or more	0.77(0.43,1.38)	0.252
Hospitalized, not requiring supplemental oxygen	3/121(2.5)	4/104(3.8)	Interaction	1.13(0.47,2.72)	0.731
Hospitalized, requiring supplemental oxygen	1/121(0.8)	1/104(1.0)			
Hospitalized, on invasive mechanical ventilation or ECMO	6/121(5.0)	3/104(2.9)			
Death	2/121(1.7)	6/104(5.8)			
Missing	2/121(1.7)				
65 years and more					
Not Hospitalized, no limitations on activities	11/93(11.8)	11/86(12.8)			
Not Hospitalized, limitations on activities	51/93(54.8)	39/86(45.3)			
Hospitalized, not requiring supplemental oxygen	8/93(8.6)	3/86(3.5)			
Hospitalized, requiring supplemental oxygen		5/86(5.8)			
Hospitalized, on non-invasive ventilation or high flow oxygen devices	1/93(1.1)				
Hospitalized, on invasive mechanical ventilation or ECMO		2/86(2.3)			
Death	21/93(22.6)	23/86(26.7)			
Missing	1/93(1.1)	3/86(3.5)			

*Adjusted for minimization variables; age and site (using clustered standard errors)

Sex at birth: (a) Male and (b) Female

Table S3 shows the subgroup analysis for gender. Overall, there was no evidence that the treatment effect was moderated by gender: interaction effect 0.91 (0.33, 2.51); p-value = 0.807.

Table S3: Subgroup analysis for gender

	Placebo	Brensocatib	Gender	Effect size (99% CI)	p value
Male					
Not hospitalized, no limitations on activities	25/127(19.7)	22/125(17.6)	Male	0.76(0.40,1.43)	0.263
Not hospitalized, limitations on activities	71/127(55.9)	66/125(52.8)	Female	0.69(0.40,1.19)	0.081
Hospitalized, not requiring supplemental oxygen	7/127(5.5)	5/125(4.0)	Interaction	0.91(0.33,2.51)	0.807
Hospitalized, requiring supplemental oxygen	1/127(0.8)	5/125(4.0)			
Hospitalized, on non-invasive ventilation or high flow oxygen devices	1/127(0.8)				
Hospitalized, on invasive mechanical ventilation or ECMO	5/127(3.9)	3/125(2.4)			
Death	15/127(11.8)	23/125(18.4)			
Missing	2/127(1.6)	1/125(0.8)			
Female					
Not hospitalized, no limitations on activities	15/87(17.2)	6/65(9.2)			
Not hospitalized, limitations on activities	58/87(66.7)	46/65(70.8)			
Hospitalized, not requiring supplemental oxygen	4/87(4.6)	2/65(3.1)			
Hospitalized, requiring supplemental oxygen		1/65(1.5)			
Hospitalized, on invasive mechanical ventilation or ECMO	1/87(1.1)	2/65(3.1)			
Death	8/87(9.2)	6/65(9.2)			

Missing	1/87(1.1)	2/65(3.1)

*Adjusted for minimization variables; age and site (using clustered standard errors)

Baseline 7-point ordinal scale: (a) 3, (b) 4 and (c) 5

Table S4 shows the subgroup analysis for baseline 7-point ordinal scale. Overall, there was no evidence that the treatment effect was moderated by baseline ordinal scale: interaction effect 1 0.62 (0.20, 1.87); p-value = 0.261 and interaction 2 1.73(0.45, 6.65); p-value=0.293.

Table S4: Subgroup analysis for baseline 7-point ordinal scale

	Placebo	Brensocatib	Baseline CSTAT	Effect size (99% CI)	p value
Baseline CSTAT = 3					
Not hospitalized, no limitations on activities	12/50(24.0)	9/42(21.4)	Baseline CSTAT = 3	0.94(0.41,2.15)	0.838
Not hospitalized, limitations on activities	32/50(64.0)	29/42(69.0)	Baseline CSTAT = 4	0.58(0.35,0.94)	0.004
Hospitalized, not requiring supplemental oxygen	4/50(8.0)	1/42(2.4)	Interaction 1	0.62(0.20,1.87)	0.261
Death	1/50(2.0)	3/42(7.1)	Baseline CSTAT = 5	0.62(0.24,1.57)	0.184
Missing	1/50(2.0)		Interaction 2	1.73(0.45,6.65)	0.293
Baseline CSTAT = 4					
Not hospitalized, no limitations on activities	27/140(19.3)	17/128(13.3)			
Not hospitalized, limitations on activities	86/140(61.4)	73/128(57.0)			
Hospitalized, not requiring supplemental oxygen	6/140(4.3)	5/128(3.9)			
Hospitalized, requiring supplemental oxygen		5/128(3.9)			
Hospitalized, on non-invasive ventilation or high flow oxygen devices	1/140(0.7)				
Hospitalized, on invasive mechanical ventilation or ECMO	4/140(2.9)	4/128(3.1)			
Death	15/140(10.7)	21/128(16.4)			
Missing	1/140(0.7)	3/128(2.3)			

Baseline CSTAT = 5		
Not hospitalized, no limitations on activities	1/24(4.2)	2/20(10.0)
Not hospitalized, limitations on activities	11/24(45.8)	10/20(50.0)
Hospitalized, not requiring supplemental oxygen	1/24(4.2)	1/20(5.0)
Hospitalized, requiring supplemental oxygen	1/24(4.2)	1/20(5.0)
Hospitalized, on invasive mechanical ventilation or ECMO	2/24(8.3)	1/20(5.0)
Death	7/24(29.2)	5/20(25.0)
Missing	1/24(4.2)	

*Adjusted for minimization variables; age and site (using clustered standard errors)

Co-enrolment into RECOVERY: (a) Yes and (b) No

Table S5 shows the subgroup analysis for co-enrolment into RECOVERY trial. Overall, there was no evidence that the treatment effect was moderated by co-enrolment into RECOVERY trial: interaction effect 0.78 (0.41, 1.50); p-value = 0.327.

Table S5: Subgroup analysis for co-enrolment into RECOVERY

	Placebo	Brensocatib	Enrolment	Effect size (99% CI)	p value
Not enrolled in RECOVERY					
Not hospitalized, no limitations on activities	25/149(16.8)	21/142(14.8)	Not enrolled	0.78(0.54,1.13)	0.081
Not hospitalized, limitations on activities	88/149(59.1)	85/142(59.9)	Enrolled	0.61(0.36,1.04)	0.017
Hospitalized, not requiring supplemental oxygen	10/149(6.7)	4/142(2.8)	Interaction	0.78(0.41,1.50)	0.327
Hospitalized, requiring supplemental oxygen	1/149(0.7)	4/142(2.8)			
Hospitalized, on non-invasive ventilation or high flow oxygen devices	1/149(0.7)				

Hospitalized, on invasive mechanical ventilation or ECMO	5/149(3.4)	3/142(2.1)
Death	16/149(10.7)	23/142(16.2)
Missing	3/149(2.0)	2/142(1.4)
Enrolled in RECOVERY		
Not hospitalized, no limitations on activities	15/65(23.1)	7/48(14.6)
Not hospitalized, limitations on activities	41/65(63.1)	27/48(56.3)
Hospitalized, not requiring supplemental oxygen	1/65(1.5)	3/48(6.3)
Hospitalized, requiring supplemental oxygen		2/48(4.2)
Hospitalized, on invasive mechanical ventilation or ECMO	1/65(1.5)	2/48(4.2)
Death	7/65(10.8)	6/48(12.5)
Missing		1/48(2.1)

*Adjusted for minimization variables; age and site (using clustered standard errors)

Symptom duration (days): (a) <10 and (b) ≥10

Table S6 shows the subgroup analysis for duration of COVID symptoms. Overall, there was no evidence that the treatment effect was moderated by duration of COVID symptoms: interaction effect 1.51 (0.35, 6.41); p-value = 0.467.

Table S6: Subgroup analysis for duration of symptoms

	Placebo	Brensocatib	Duration of symptom	Effect size (99% CI)	p value
Less than 10 days					
Not hospitalized, no limitations on activities	27/136(19.9)	12/102(11.8)	Less than 10 days	0.60(0.33,1.08)	0.026
Not hospitalized, limitations on activities	76/136(55.9)	58/102(56.9)	10 days or more	0.90(0.33,2.46)	0.787

Hospitalized, not requiring supplemental oxygen	7/136(5.1)	4/102(3.9)	Interaction	1.51(0.35,6.41)	0.467
Hospitalized, requiring supplemental oxygen	1/136(0.7)	5/102(4.9)			
Hospitalized, on non-invasive ventilation or high flow oxygen devices	1/136(0.7)				
Hospitalized, on invasive mechanical ventilation or ECMO	5/136(3.7)	4/102(3.9)			
Death	16/136(11.8)	17/102(16.7)			
Missing	3/136(2.2)	2/102(2.0)			
10 days or more					
Not hospitalized, no limitations on activities	13/78(16.7)	16/88(18.2)			
Not hospitalized, limitations on activities	53/78(67.9)	54/88(61.4)			
Hospitalized, not requiring supplemental oxygen	4/78(5.1)	3/88(3.4)			
Hospitalized, requiring supplemental oxygen		1/88(1.1)			
Hospitalized, on invasive mechanical ventilation or ECMO	1/78(1.3)	1/88(1.1)			
Death	7/78(9.0)	12/88(13.6)			
Missing		1/88(1.1)			

*Adjusted for minimization variables; age and site (using clustered standard errors)

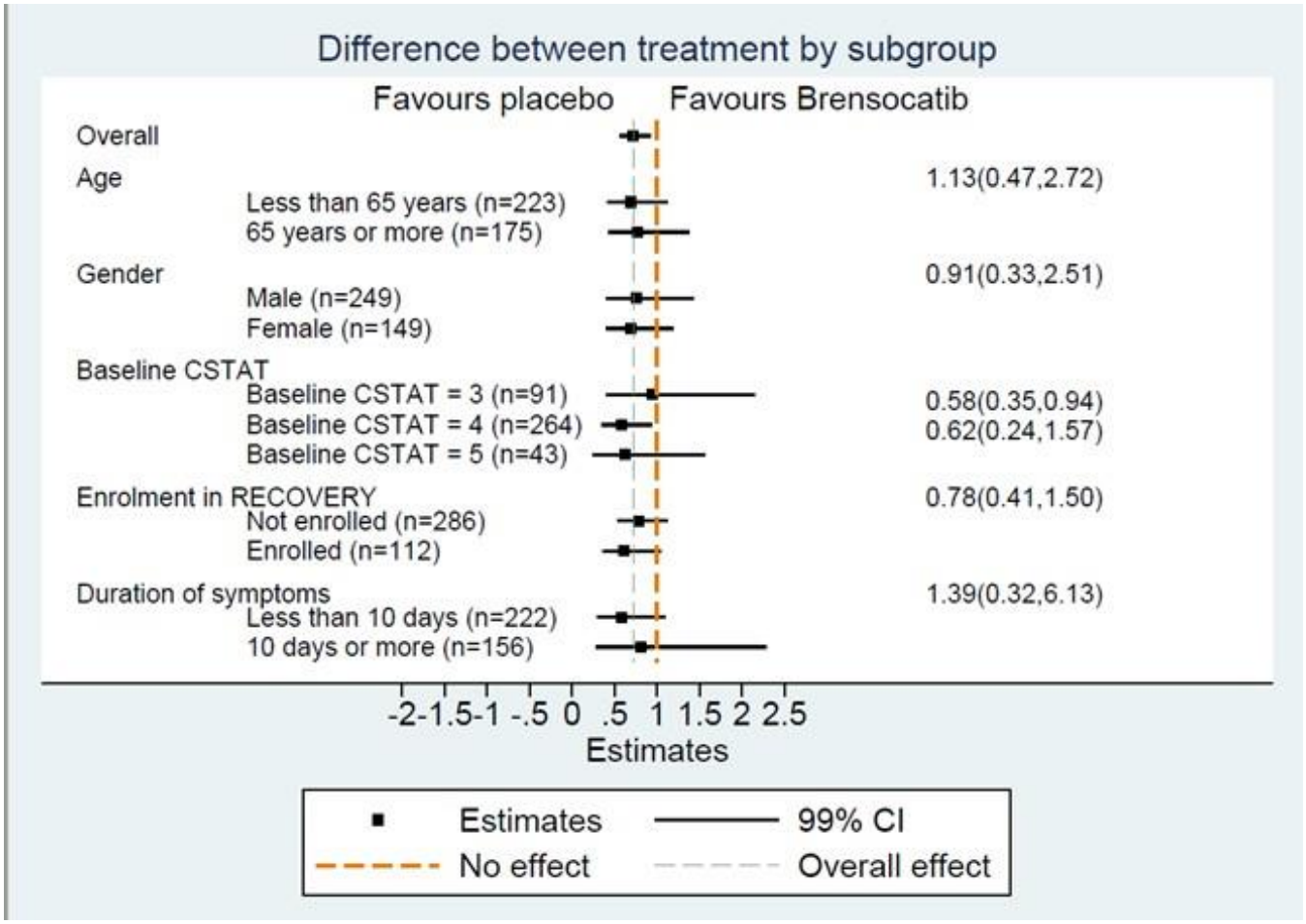

Figure S1: Forest plot for each subgroup. N=398 as 6 participants were lost to follow-up

Per-protocol analysis

In total, there were 71 participants (35 in placebo arm and 36 in Brensocatib arm) who discontinued trial drug during the study period. After excluding these participants, 179 participants in the placebo arm and 154 in Brensocatib arm were included in the per-protocol analysis. Table S7 shows the pre-protocol analysis. The unadjusted odds ratio (95% confidence interval) from a proportional odds model was 0.81 (0.52 to 1.25).

Table S7: Per-protocol analysis for primary outcome

	Placebo N=179	Brensocatib N=154	Model	Effect size (95% CI)	p value
Not hospitalized, no limitations on activities	33 (18.4)	24 (15.6)	Unadjusted Model	0.81(0.52,1.25)	0.340

Not hospitalized, limitations on activities	116 (64.8)	99 64.3)	Adjusted Model*	0.79(0.60,1.06)	0.114
Hospitalized, not requiring supplemental oxygen	9 (5.0)	6 (3.9)	Adjusted Model[#] for additional	0.81(0.61,1.08)	0.149
Hospitalized, requiring supplemental oxygen	1 (0.6)	6 (3.9)	variables		
Hospitalized, on invasive mechanical ventilation or ECMO	2 (1.1)	1 (0.6)			
Death	17 (9.5)	17 (11.0)			
Missing	1 (0.6)	1 (0.6)			

*Adjusted for minimization variables; age and site (using clustered standard errors)

[#] Adjusted for gender, hypertension, and chronic obstructive pulmonary disease and minimization variables; age and site (using clustered standard errors

Clinical status at Day 3, 5, 8, 11 and 15

The number and percentage of participants in each clinical status category for day 3, 5, 8, 11 and 15 are summarized and reported in Table S8.

Table S8: Clinical status at day 3, 5, 8, 11 and 15

		Placebo N=214	Brensocatib N=190
Day 3	Not hospitalized, no limitations on activities	3(1.4)	2(1.1)
	Not hospitalized, limitations on activities	35(16.4)	21(11.1)
	Hospitalized, not requiring supplemental oxygen	45(21.0)	41(21.6)
	Hospitalized, requiring supplemental oxygen	93(43.5)	90(47.4)
	Hospitalized, on non-invasive ventilation or high flow oxygen devices	33(15.4)	32(16.8)
	Hospitalized, on invasive mechanical ventilation or ECMO	1(0.5)	3(1.6)
	Death	3(1.4)	
	Missing	1(0.5)	1(0.5)
Day 5	Not hospitalized, no limitations on activities	4(1.9)	6(3.2)
	Not hospitalized, limitations on activities	68(31.8)	51(26.8)
	Hospitalized, not requiring supplemental oxygen	46(21.5)	38(20.0)
	Hospitalized, requiring supplemental oxygen	59(27.6)	53(27.9)

	Hospitalized, on non-invasive ventilation or high flow oxygen devices	24(11.2)	33(17.4)
	Hospitalized, on invasive mechanical ventilation or ECMO	5(2.3)	5(2.6)
	Death	6(2.8)	2(1.1)
	Missing	2(0.9)	2(1.1)
Day 8	Not hospitalized, no limitations on activities	18(8.4)	9(4.7)
	Not hospitalized, limitations on activities	98(45.8)	84(44.2)
	Hospitalized, not requiring supplemental oxygen	27(12.6)	23(12.1)
	Hospitalized, requiring supplemental oxygen	37(17.3)	34(17.9)
	Hospitalized, on non-invasive ventilation or high flow oxygen devices	17(7.9)	18(9.5)
	Hospitalized, on invasive mechanical ventilation or ECMO	6(2.8)	7(3.7)
	Death	9(4.2)	11(5.8)
	Missing	2(0.9)	4(2.1)
Day 11	Not hospitalized, no limitations on activities	18(8.4)	14(7.4)
	Not hospitalized, limitations on activities	122(57.0)	100(52.6)
	Hospitalized, not requiring supplemental oxygen	20(9.3)	14(7.4)
	Hospitalized, requiring supplemental oxygen	22(10.3)	24(12.6)
	Hospitalized, on non-invasive ventilation or high flow oxygen devices	7(3.3)	6(3.2)
	Hospitalized, on invasive mechanical ventilation or ECMO	8(3.7)	10(5.3)
	Death	14(6.5)	16(8.4)
	Missing	3(1.4)	6(3.2)
Day 15	Not hospitalized, no limitations on activities	26(12.1)	22(11.6)
	Not hospitalized, limitations on activities	124(57.9)	103(54.2)
	Hospitalized, not requiring supplemental oxygen	19(8.9)	12(6.3)
	Hospitalized, requiring supplemental oxygen	13(6.1)	16(8.4)
	Hospitalized, on non-invasive ventilation or high flow oxygen devices	5(2.3)	3(1.6)
	Hospitalized, on invasive mechanical ventilation or ECMO	6(2.8)	9(4.7)
	Death	18(8.4)	20(10.5)
	Missing	3(1.4)	5(2.6)

*Numbers in cells are n(%)

Table S9- neutrophil elastase activity (substudy at Dundee and Sheffield sites only).

	Placebo N=214	Brensocatib N=190	Effect estimate (95% CI)
Day 1	132 (86);[N=77]	134 (113);[N=75]	n/a
Day 8	163 (102);[N=32]	131 (64);[N=25]	-40 (-84, 5)
Day 15	167 (127);[N=13]	85 (69);[N=16]	-83 (-141, -23)
Day 29	166 (97);[N=48]	103 (65);[N=50]	-67 (-102, -31)

Cells are mean, (SD) [N}, effect estimates come from a linear repeated measures mixed model and estimate the difference between groups at each time point.

Adverse events, system organ class (SOC) and preferred term level

Tables S10 and S11 show the adverse events reported during the study. Overall, 185 participants (99 (46.3%) in placebo arm and 86 (44.8%) in Brensocatib arm) reported at least one adverse event (IRR: 0.97 (95% CI 0.73, 1.29); p=0.827). There were in total, 296 events; 164 in placebo and 132 in Brensocatib. The most common adverse events were gastrointestinal disorders and infections and infestations.

Table S10: Adverse events and system organ class

	Placebo N=214	Brensocatib N=192
Number of participants with no adverse events	115(53.7)	106(55.2)
Number of participants with adverse events	99(46.3)	86(44.8)

Number of adverse events	164	132
Severity		
Mild	95(57.9)	67(50.8)
Moderate	35(21.3)	23(17.4)
Severe	34(20.7)	42(31.8)
System Organ Class level		
Blood and lymphatic system disorders	1(0.6)	0
Cardiac disorders	4(2.4)	7(5.3)
Eye disorders	2(1.2)	2(1.5)
Gastrointestinal disorders	43(26.2)	19(14.4)
General disorders and administration site conditions	7(4.3)	8(6.1)
Hepatobiliary disorders	1(0.6)	1(0.8)
Infections and infestations	33(20.1)	33(25.0)
Injury, poisoning and procedural complications	0	1(0.8)
Investigations	7(4.3)	6(4.5)
Metabolism and nutrition disorders	5(3.0)	5(3.8)
Musculoskeletal and connective tissue disorders	8(4.9)	4(3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(0.6)	1(0.8)
Nervous system disorders	12(7.3)	11(8.3)
Psychiatric disorders	6(3.7)	2(1.5)
Renal and urinary disorders	4(2.4)	2(1.5)
Respiratory, thoracic and mediastinal disorders	13(7.9)	16(12.1)
Skin and subcutaneous tissue disorders	16(9.8)	12(9.1)
Vascular disorders	1(0.6)	2(1.5)

*Numbers in cells are n(%)

Table S11: Summary of all adverse events – Preferred Term Level

	Placebo N=214	Brensocatib N=192
Number of participants with no adverse events	115(53.7)	106(55.2)
Number of participants with adverse events	99(46.3)	86(44.8)
Number of adverse events	164	132
Preferred Term Level		
Abdominal pain	5(3.0)	0

Acne	1(0.6)	0
Acute coronary syndrome	0	1(0.8)
Acute kidney injury	1(0.6)	2(1.5)
Alanine aminotransferase increased	4(2.4)	2(1.5)
Anaemia	1(0.6)	0
Arthralgia	4(2.4)	2(1.5)
Arthritis bacterial	0	1(0.8)
Atrial fibrillation	2(1.2)	0
Back pain	0	1(0.8)
Blood glucose abnormal	1(0.6)	1(0.8)
Blood glucose increased	1(0.6)	0
Bradycardia	1(0.6)	1(0.8)
COVID-19	17(10.4)	13(9.8)
COVID-19 pneumonia	2(1.2)	9(6.8)
Candida infection	0	1(0.8)
Cerebellar infarction	0	1(0.8)
Cerebral infarction	0	1(0.8)
Cerebrovascular accident	0	1(0.8)
Chest discomfort	0	2(1.5)
Chest pain	3(1.8)	0
Cholelithiasis	1(0.6)	0
Chronic lymphocytic leukaemia	0	1(0.8)
Clostridium difficile infection	0	1(0.8)
Cold sweat	1(0.6)	0
Constipation	4(2.4)	1(0.8)
Coronavirus infection	0	1(0.8)
Deep vein thrombosis	1(0.6)	0
Delirium	3(1.8)	0
Diarrhoea	2(1.2)	0
Diverticulitis	1(0.6)	0
Dizziness	5(3.0)	3(2.3)
Drug eruption	0	1(0.8)
Dry mouth	2(1.2)	1(0.8)
Dry skin	1(0.6)	2(1.5)
Dysarthria	1(0.6)	0
Dyspepsia	4(2.4)	3(2.3)
Dyspnoea	4(2.4)	1(0.8)
Dysuria	1(0.6)	0

Eczema	1(0.6)	0
Electrocardiogram abnormal	1(0.6)	0
Epistaxis	0	3(2.3)
Extravasation	0	1(0.8)
Eye pruritus	1(0.6)	0
Fall	0	1(0.8)
Feeling hot	1(0.6)	0
Flatulence	1(0.6)	0
Gastritis erosive	0	1(0.8)
Gastroesophageal reflux disease	1(0.6)	1(0.8)
Gingival bleeding	0	1(0.8)
Gingival pain	1(0.6)	0
Glossodynia	1(0.6)	1(0.8)
Glycosylated haemoglobin increased	0	1(0.8)
Gout	1(0.6)	0
Hallucination, visual	0	1(0.8)
Headache	2(1.2)	2(1.5)
Hepatic function abnormal	0	1(0.8)
Hiccups	1(0.6)	2(1.5)
Hyperglycaemia	2(1.2)	4(3.0)
Hyperhidrosis	1(0.6)	0
Hypoaesthesia	1(0.6)	0
Hypoaesthesia oral	0	1(0.8)
Hypokalaemia	0	1(0.8)
Hypomagnesaemia	1(0.6)	0
Hypoxia	0	1(0.8)
Insomnia	2(1.2)	0
Interstitial lung disease	1(0.6)	0
Intestinal ischaemia	0	1(0.8)
Lip pain	0	1(0.8)
Lip swelling	1(0.6)	0
Liver function test abnormal	0	1(0.8)
Lower gastrointestinal haemorrhage	1(0.6)	0
Lower respiratory tract infection	2(1.2)	1(0.8)
Malaise	1(0.6)	0
Memory impairment	0	1(0.8)
Metastases to liver	1(0.6)	0
Mouth ulceration	1(0.6)	2(1.5)

Multiple organ dysfunction syndrome	0	1(0.8)
Muscle spasms	0	1(0.8)
Musculoskeletal pain	1(0.6)	0
Nausea	3(1.8)	3(2.3)
Neck pain	1(0.6)	0
Night sweats	1(0.6)	0
Nightmare	0	1(0.8)
Non-cardiac chest pain	1(0.6)	0
Oedema peripheral	1(0.6)	1(0.8)
Oesophagitis	1(0.6)	0
Oral candidiasis	3(1.8)	0
Oral mucosal blistering	1(0.6)	0
Oral mucosal eruption	1(0.6)	0
Oral pain	1(0.6)	0
Pain in jaw	1(0.6)	0
Palpitations	0	2(1.5)
Pancreatic cyst	1(0.6)	0
Paraesthesia	0	1(0.8)
Paraesthesia oral	1(0.6)	0
Peripheral ischaemia	0	2(1.5)
Peripheral swelling	0	2(1.5)
Pharyngitis	1(0.6)	0
Plantar fasciitis	1(0.6)	0
Pneumonia	1(0.6)	2(1.5)
Pneumonitis	1(0.6)	0
Pneumothorax	1(0.6)	3(2.3)
Pneumothorax spontaneous	0	1(0.8)
Pollakiuria	2(1.2)	0
Pruritus	1(0.6)	1(0.8)
Pulmonary embolism	5(3.0)	4(3.0)
Rash	7(4.3)	5(3.8)
Rash macular	1(0.6)	0
Rash pruritic	1(0.6)	1(0.8)
Rash pustular	1(0.6)	0
Rectal haemorrhage	1(0.6)	0
Respiratory tract infection	1(0.6)	0
Right ventricular failure	1(0.6)	0
Serratia infection	0	1(0.8)

Sinus bradycardia	0	1(0.8)
Sputum increased	0	1(0.8)
Staphylococcal bacteraemia	0	1(0.8)
Steroid diabetes	1(0.6)	0
Subarachnoid haemorrhage	0	1(0.8)
Subcutaneous emphysema	0	1(0.8)
Suicidal ideation	1(0.6)	0
Supraventricular tachycardia	0	1(0.8)
Swelling face	0	1(0.8)
Swollen tongue	1(0.6)	1(0.8)
Syncope	3(1.8)	0
Tachyarrhythmia	0	1(0.8)
Tongue blistering	1(0.6)	0
Tongue discolouration	1(0.6)	0
Tongue erythema	1(0.6)	0
Toothache	1(0.6)	0
Transaminases increased	0	1(0.8)
Urinary tract infection	1(0.6)	2(1.5)
Urosepsis	1(0.6)	0
Urticaria	0	1(0.8)
Vision blurred	1(0.6)	2(1.5)
Vomiting	4(2.4)	1(0.8)
Vulvovaginal candidiasis	2(1.2)	0

*Numbers in cells are n(%)

Table S12 shows the details of the adverse events. Of 296 events reported, 64 (39.0%) in placebo arm and 48 (36.4%) were possibly due to the treatment received and 92 (56.1%) and 56(42.4%) in placebo and Brensocatib arms recovered, respectively.

Table S12: Details of adverse events

	Placebo N=214	Brensocatib N=192
Number of participants with adverse events	99(46.3)	86(44.8)
Number of adverse events	164	132
Details of adverse events		
Relationship to trial drug		

	None	98(59.8)	80(60.6)
	Probable	2(1.2)	4(3.0)
	Possible	64(39.0)	48(36.4)
Action Taken			
	IMP permanently stopped	10(6.1)	10(7.6)
	IMP temporarily stopped	2(1.2)	3(2.3)
	Others	22(13.4)	19(14.4)
	Hospitalisation, IMP temporarily stopped	1(0.6)	0
	Hospitalisation, Con meds commenced, Others	1(0.6)	0
	IMP temporarily stopped, Others	0	1(0.8)
	Con meds commenced	38(23.2)	24(18.2)
	IMP permanently stopped, Con meds commenced	0	2(1.5)
	Hospitalisation, Con meds commenced	1(0.6)	0
	Hospitalisation	9(5.5)	6(4.5)
	Con meds commenced, Others	0	1(0.8)
	None	79(48.2)	65(49.2)
	Missing	1(0.6)	1(0.8)
Outcome			
	Recovering	13(7.9)	17(12.9)
	Recovered with sequelae	1(0.6)	4(3.0)
	Recovered	92(56.1)	56(42.4)
	Unknown	7(4.3)	2(1.5)
	Not recovered	27(16.5)	25(18.9)
	Fatal	24(14.6)	28(21.2)

*Numbers in cells are n(%)

Serious adverse events and system organ class level

Of 406 participants, 75 (18.5%) had at least one serious adverse event; 35 (16.4%) in placebo arm and 40 (20.8%) in Brensocatib arm (IRR: 1.27 (95%CI 0.81, 2.01); p=0.30). There were 81 SAEs in total; 39 in placebo arm and 42 in Brensocatib arm. The most common serious adverse events were infections and infestations (table S13).

Table S13: Serious adverse events

	Placebo	Brensocatib

	N=214	N=192
Number of participants with no serious adverse events	179(83.6)	152(79.2)
Number of participants with serious adverse events	35(16.4)	40(20.8)
Number of SAEs	39	42
System Organ Class Level		
Cardiac disorders	1(2.6)	0
Gastrointestinal disorders	3(7.7)	1(2.4)
General disorders and administration site conditions	0	1(2.4)
Infections and infestations	23(59.0)	26(61.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(2.6)	0
Nervous system disorders	2(5.1)	4(9.5)
Psychiatric disorders	2(5.1)	0
Renal and urinary disorders	1(2.6)	0
Respiratory, thoracic and mediastinal disorders	5(12.8)	7(16.7)
Skin and subcutaneous tissue disorders	0	2(4.8)
Vascular disorders	1(2.6)	1(2.4)

*Numbers in cells are n(%)

Table S14: Causes of death and relatedness to study drug

		Placebo N=23	Brensocatib N=29
Relationship with the trial drug	None	22(95.7)	29(100.0)
	Possible	1(4.3)	
Cause of death	COVID-19	17(73.9)	12(41.4)
	COVID-19 pneumonia	2(8.7)	9(31.0)
	Cerebellar infarction		1(3.4)
	Coronavirus infection		1(3.4)
	Interstitial lung disease	1(4.3)	
	Intestinal ischaemia		1(3.4)
	Lower respiratory tract infection	1(4.3)	
	Carcinoma with metastases to liver	1(4.3)	
	Multiple organ dysfunction syndrome		1(3.4)
	Pneumonia	1(4.3)	1(3.4)
	Pulmonary embolism		1(3.4)
	Subarachnoid haemorrhage		1(3.4)
	Not recorded		1 (3.4)

*Numbers in cells are n(%)

Table S15: Quality of life assessments using the EQ-5D-5L assessment tool

	Placebo (N=151)	**Brensocatib (n=190)**	**Model**	**Effect size (95% CI)**	**p-value**
Mean (SD)	0.670 (0.248)	0.674 (0.289)	Unadjusted	0.004 (-0.059,0.066	p=0.912
Median (25th, 75th centile)	0.735 (0.548,0.0837)	0.753 (0.592,0.850)	Adjusted	0.003 (-0.060,0.066)	P=0.923

*Adjusted for minimization variables; age and site (using clustered standard errors)