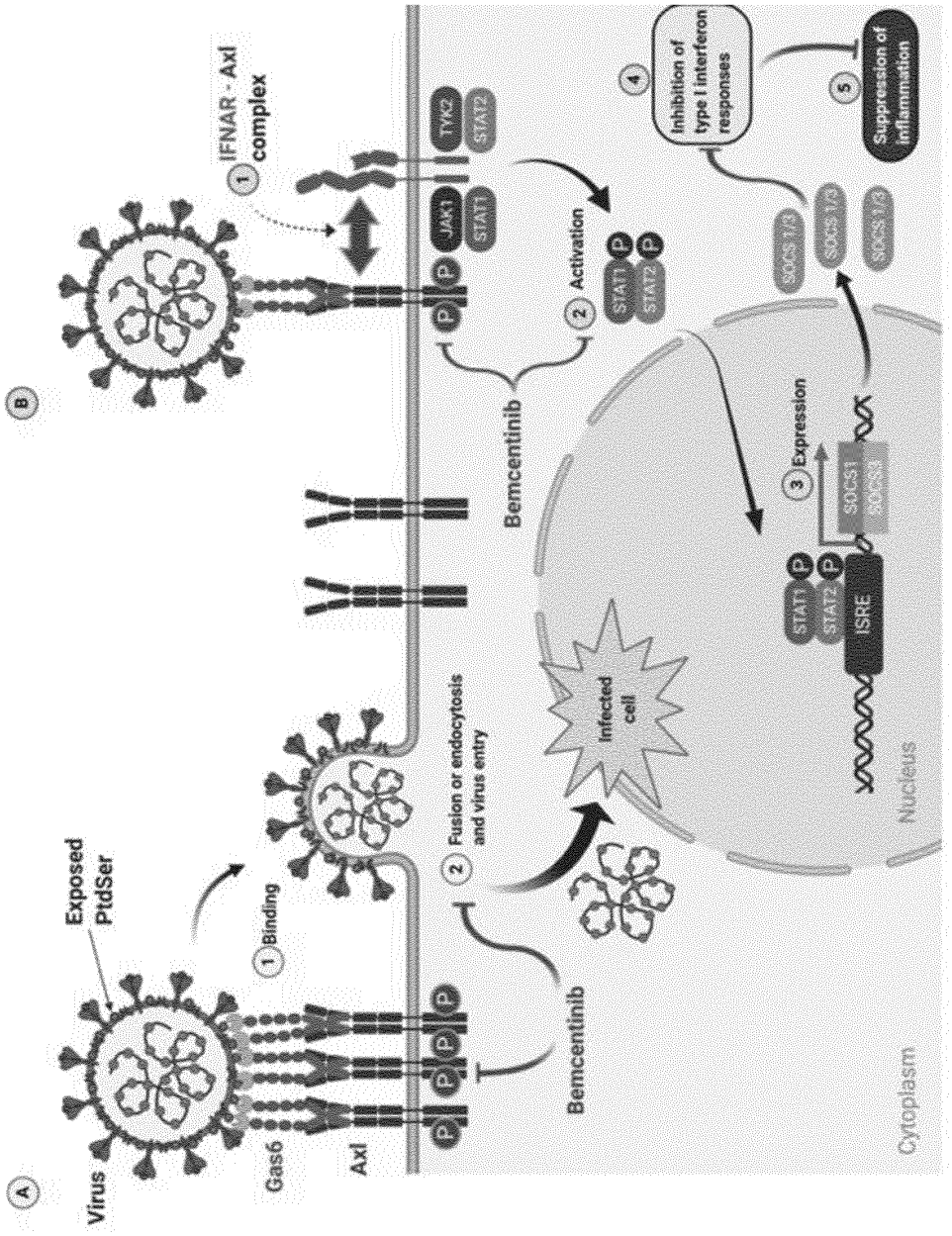

A
Virus
Exposed PtdSer
Gas6
Axl
1 Binding
2 Fusion or endocytosis and virus entry
Bemcentinib
Infected cell
B
1 IFNAR - Axl complex
TYK2
STAT2
JAK1
STAT1
2 Activation
Bemcentinib
STAT1 P
STAT2 P
3 Expression
SOCS1
SOCS3
ISRE
4 Inhibition of type I interferon responses
5 Suppression of inflammation
SOCS 1/3
Nucleus
Cytoplasm

Figure 1

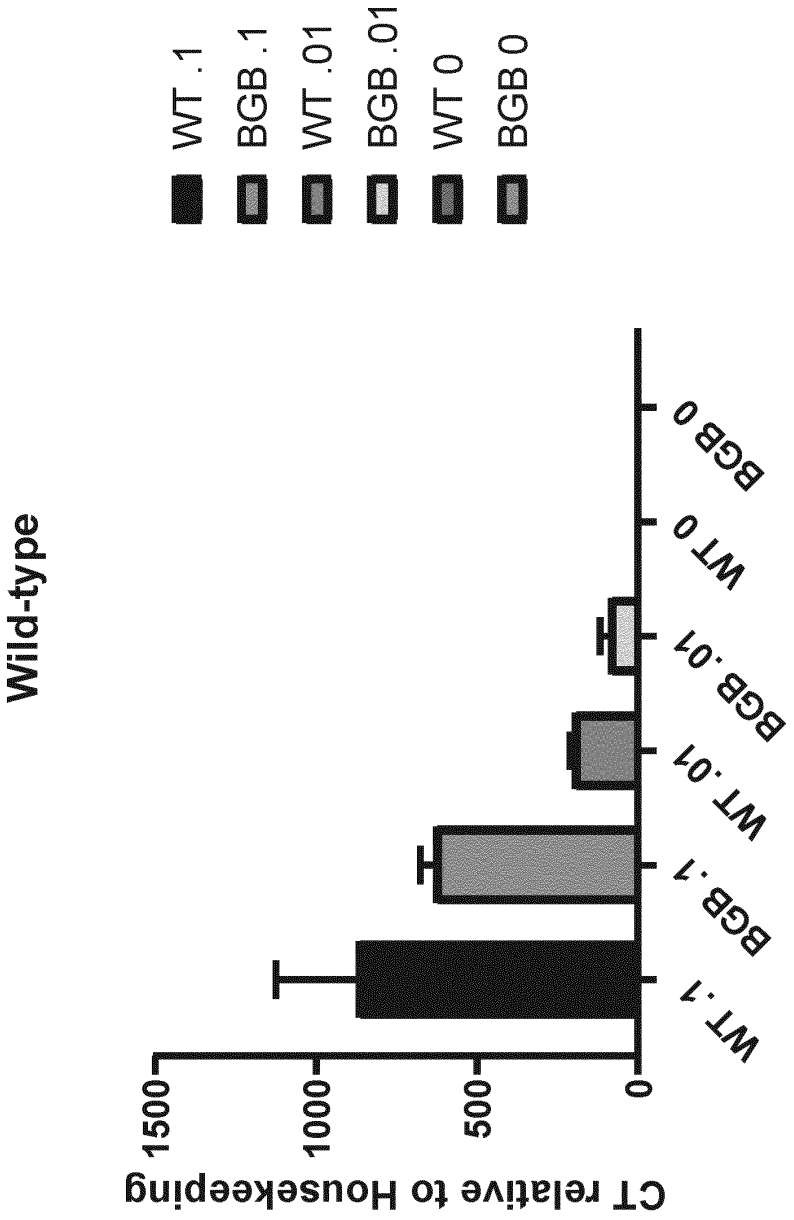

Wild-type
WT .1
BGB .1
WT .01
BGB .01
WT 0
BGB 0
CT relative to Housekeeping
1500
1000
500
0
WT .1
BGB .1
WT .01
BGB .01
WT 0
BGB 0

Figure 2A

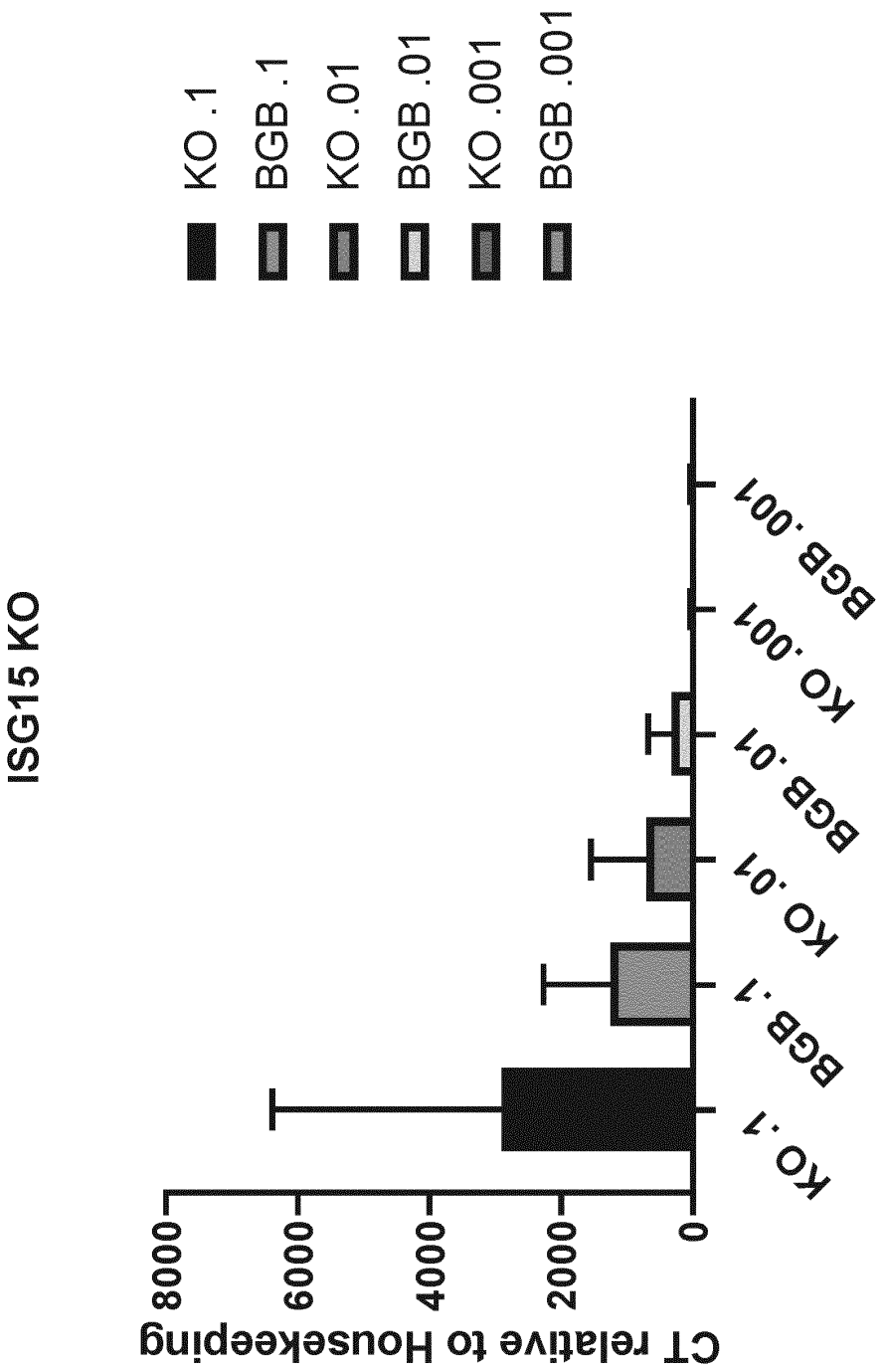
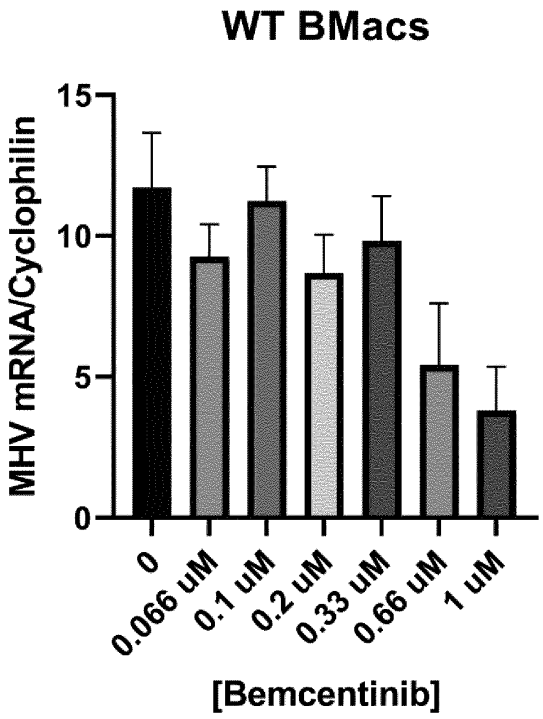

ISG15 KO
KO .1
BGB .1
KO .01
BGB .01
KO .001
BGB .001
CT relative to Housekeeping
8000
6000
4000
2000
0
KO .1
BGB .1
KO .01
BGB .01
KO .001
BGB .001

Figure 2B

A


WT BMacs
MHV mRNA/Cyclophilin
15
10
5
0
0
0.066 uM
0.1 uM
0.2 uM
0.33 uM
0.66 uM
1 uM
[Bemcentinib]

B

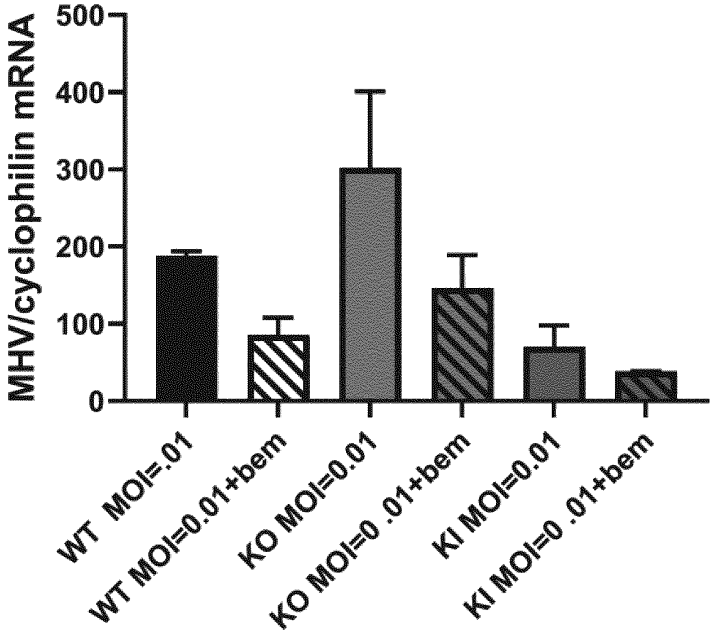

MHV/cyclophilin mRNA
500
400
300
200
100
0
WT MOI=.01
WT MOI=0.01+bem
KO MOI=0.01
KO MOI=0 .01+bem
KI MOI=0.01
KI MOI=0 .01+bem

Figure 3

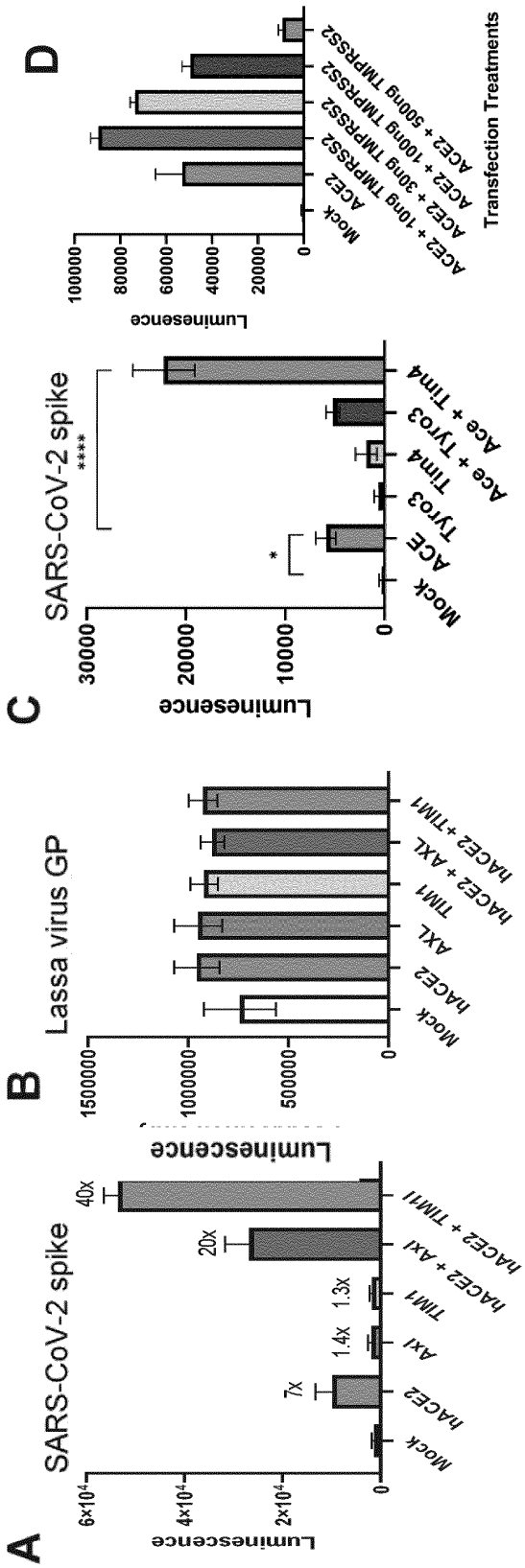

A
SARS-CoV-2 spike
Luminescence
6x10^4
4x10^4
2x10^4
0
Mock
hACE2
AXL
TIM1
hACE2 + AXL
hACE2 + TIM1
7x
1.4x
1.3x
20x
40x
B
Lassa virus GP
Luminescence
1500000
1000000
500000
0
Mock
hACE2
AXL
TIM1
hACE2 + AXL
hACE2 +TIM1
C
SARS-CoV-2 spike
Luminescence
30000
20000
10000
0
****
*
Mock
ACE
Tyro3
Tim4
Ace + Tyro3
Ace + Tim4
D
Luminescence
100000
80000
60000
40000
20000
0
Mock
ACE2
ACE2 + 10ng TMPRSS2
ACE2 + 30ng TMPRSS2
ACE2 + 100ng TMPRSS2
ACE2 + 500ng TMPRSS2
Transfection Treatments

Figure 4

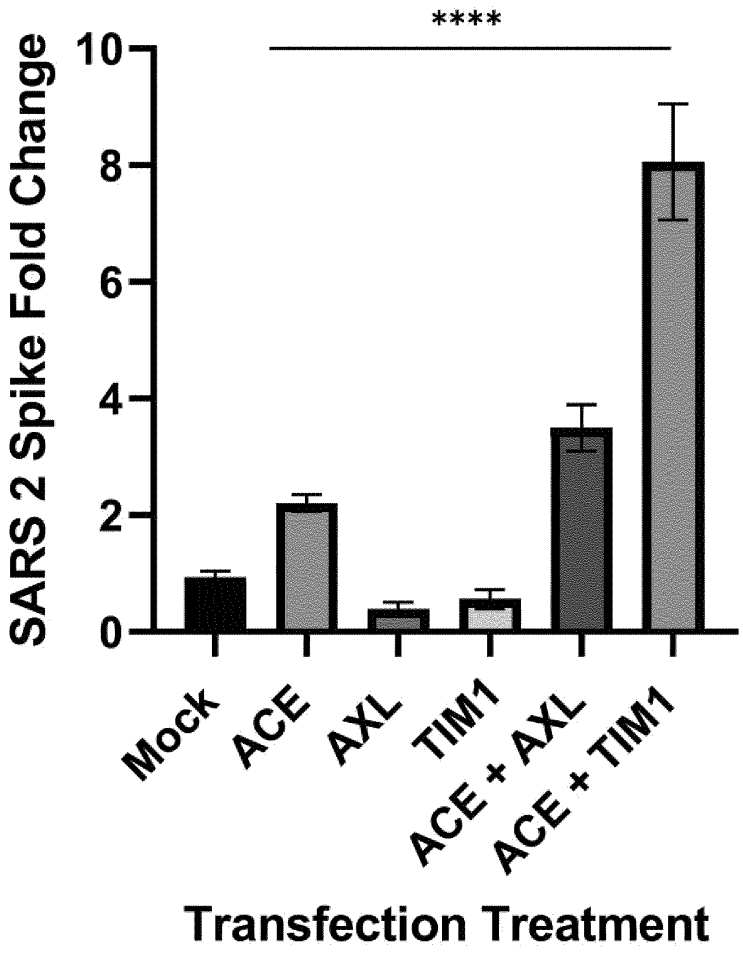

****
SARS 2 Spike Fold Change
10
8
6
4
2
0
Mock
ACE
AXL
TIM1
ACE + AXL
ACE + TIM1
Transfection Treatment

Figure 5

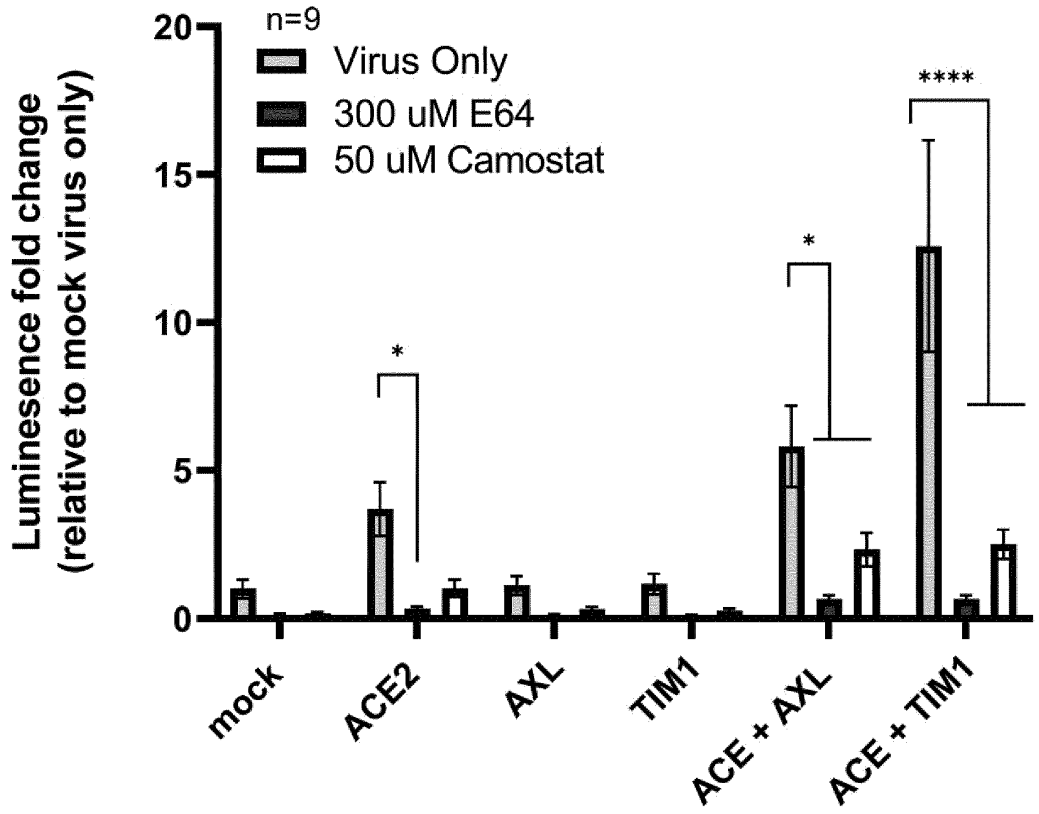

n=9
Virus Only
300 uM E64
50 uM Camostat
Luminesence fold change
(relative to mock virus only)
20
15
10
5
0
*
*
****
mock
ACE2
AXL
TIM1
ACE + AXL
ACE + TIM1

Figure 6

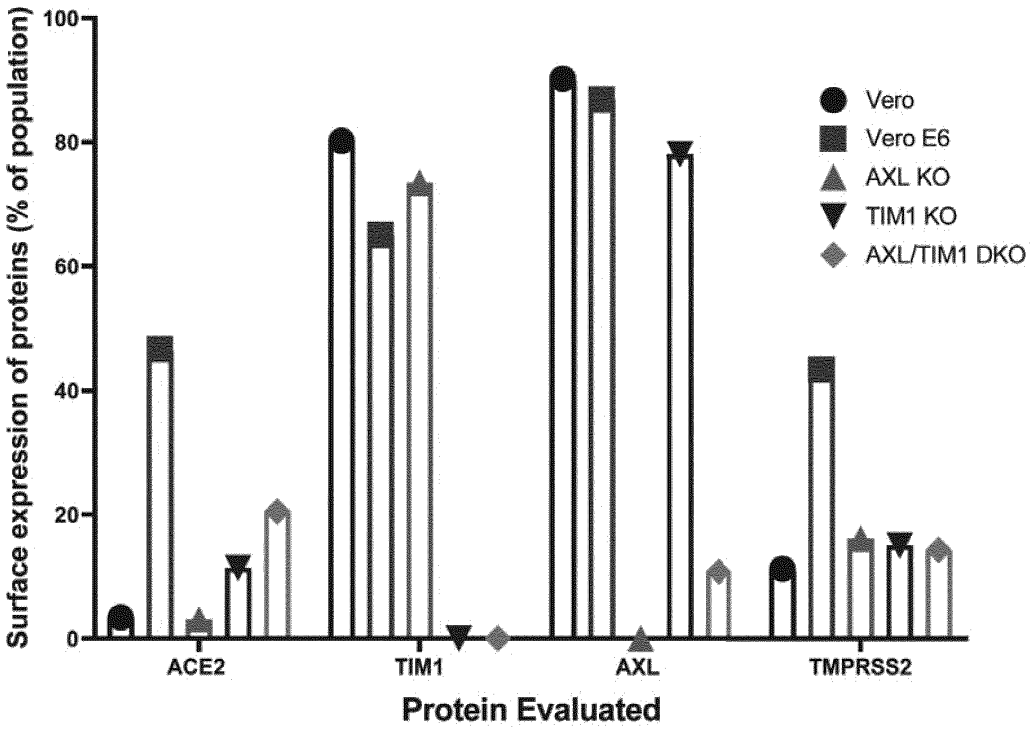

Surface expression of proteins (% of population)
100
80
60
40
20
0
ACE2
TIM1
AXL
TMPRSS2
Protein Evaluated
Vero
Vero E6
AXL KO
TIM1 KO
AXL/TIM1 DKO

Figure 7

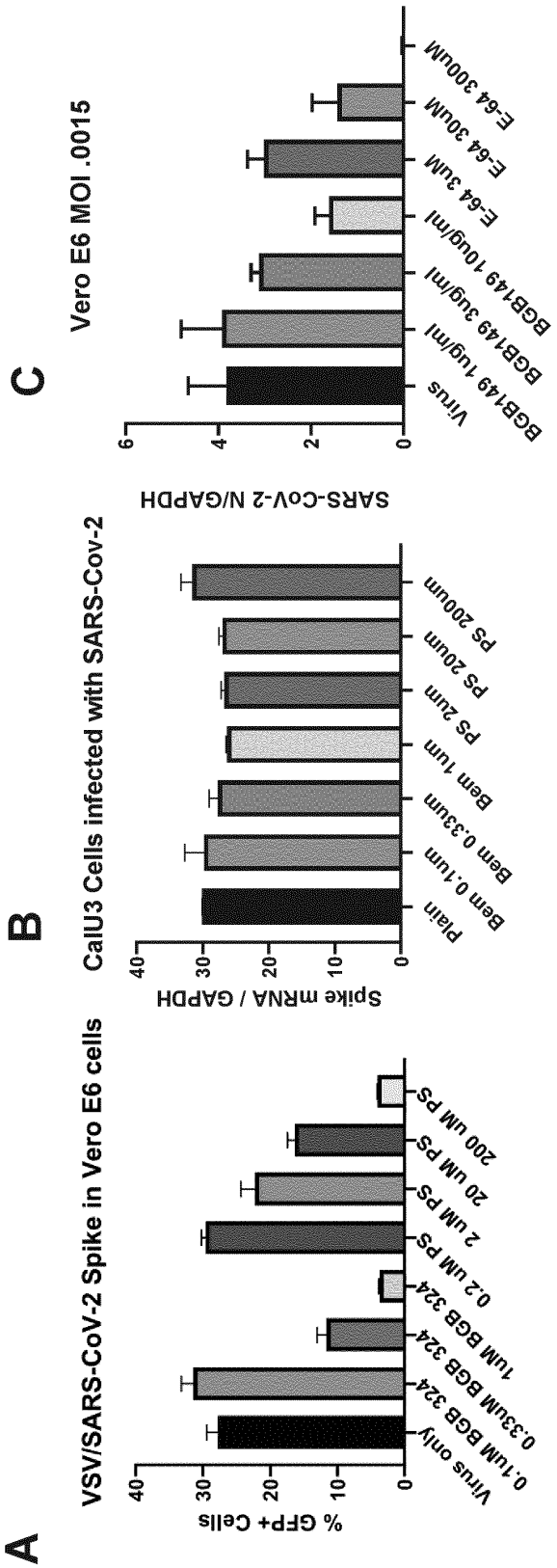

A
VSV/SARS-CoV-2 Spike in Vero E6 cells
% GFP+ Cells
0
10
20
30
40
Virus only
0.1uM BGB 324
0.33uM BGB 324
1uM BGB 324
0.2 uM PS
2 uM PS
20 uM PS
200 uM PS
B
CalU3 Cells infected with SARS-Cov-2
Spike mRNA / GAPDH
0
10
20
30
40
Plain
Bem 0.1um
Bem 0.33um
Bem 1um
PS 2um
PS 20um
PS 200um
C
Vero E6 MOI .0015
SARS-CoV-2 N/GAPDH
0
2
4
6
Virus
BGB149 1ug/ml
BGB149 3ug/ml
BGB149 10ug/ml
E-64 3uM
E-64 30uM
E-64 300uM

Figure 8

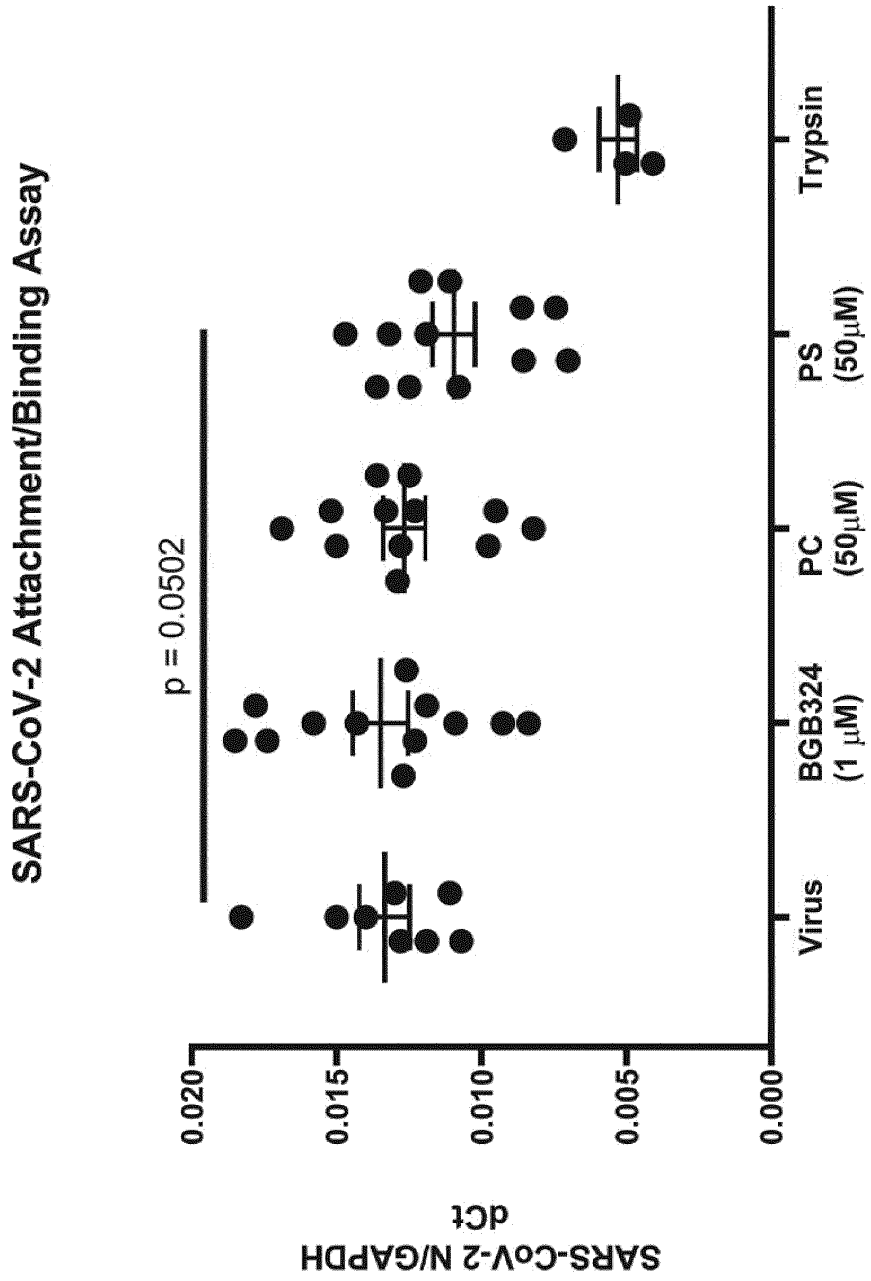

SARS-CoV-2 Attachment/Binding Assay
p = 0.0502
SARS-CoV-2 N/GAPDH dCt
0.020
0.015
0.010
0.005
0.000
Virus
BGB324 (1 μM)
PC (50μM)
PS (50μM)
Trypsin

Figure 9

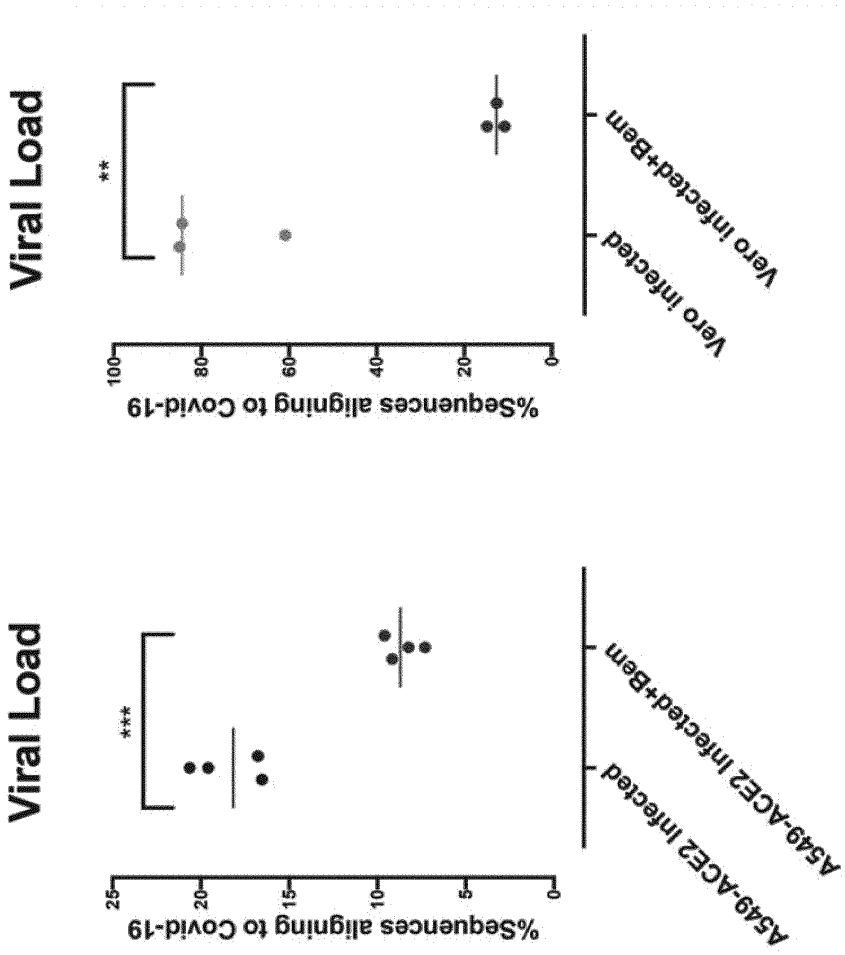

Viral Load
%Sequences aligning to Covid-19
0
5
10
15
20
25
***
A549-ACE2 Infected
A549-ACE2 Infected+Bem
Viral Load
%Sequences aligning to Covid-19
0
20
40
60
80
100
**
Vero Infected
Vero Infected+Bem

Figure 10

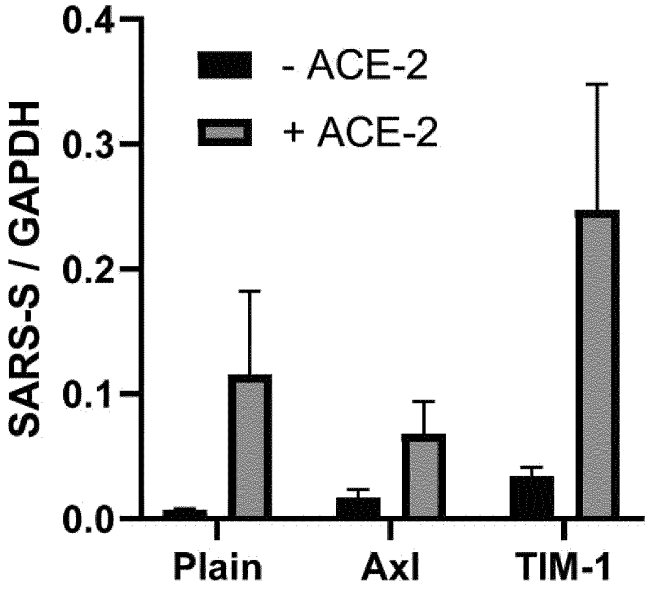



Figure 11

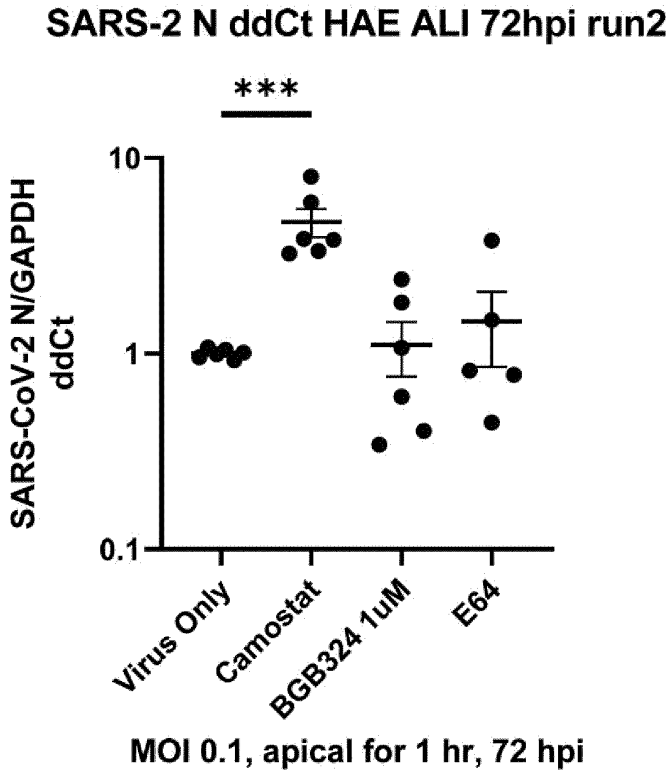
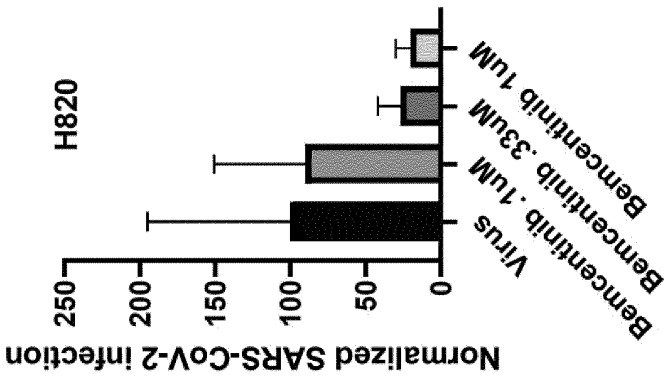
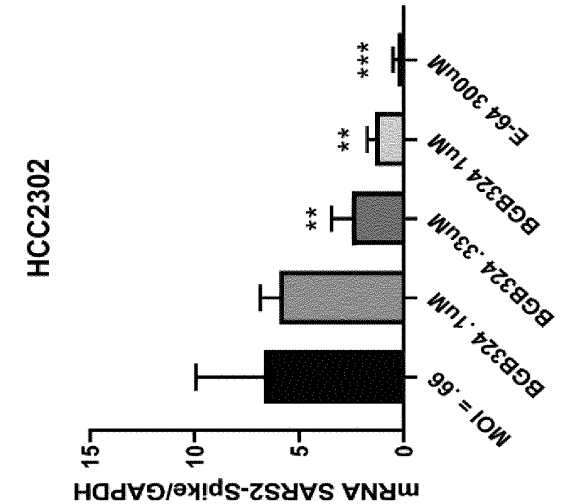



Figure 12


H820
Normalized SARS-CoV-2 infection
250
200
150
100
50
0
Virus
Bemcentinib .1uM
Bemcentinib .33uM
Bemcentinib 1uM


HCC2302
mRNA SARS2-Spike/GAPDH
15
10
5
0
MOI = .66
BGB324 .1uM
BGB324 .33uM
BGB324 1uM
E-64 300uM
**
**
***

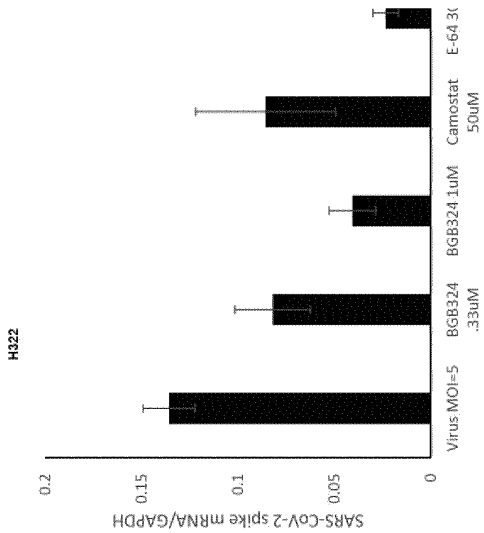

H322
SARS-CoV-2 spike mRNA/GAPDH
0.2
0.15
0.1
0.05
0
Virus MOI=5
BGB324 .33uM
BGB324 1uM
Camostat 50uM
E-64 3(

Figure 13

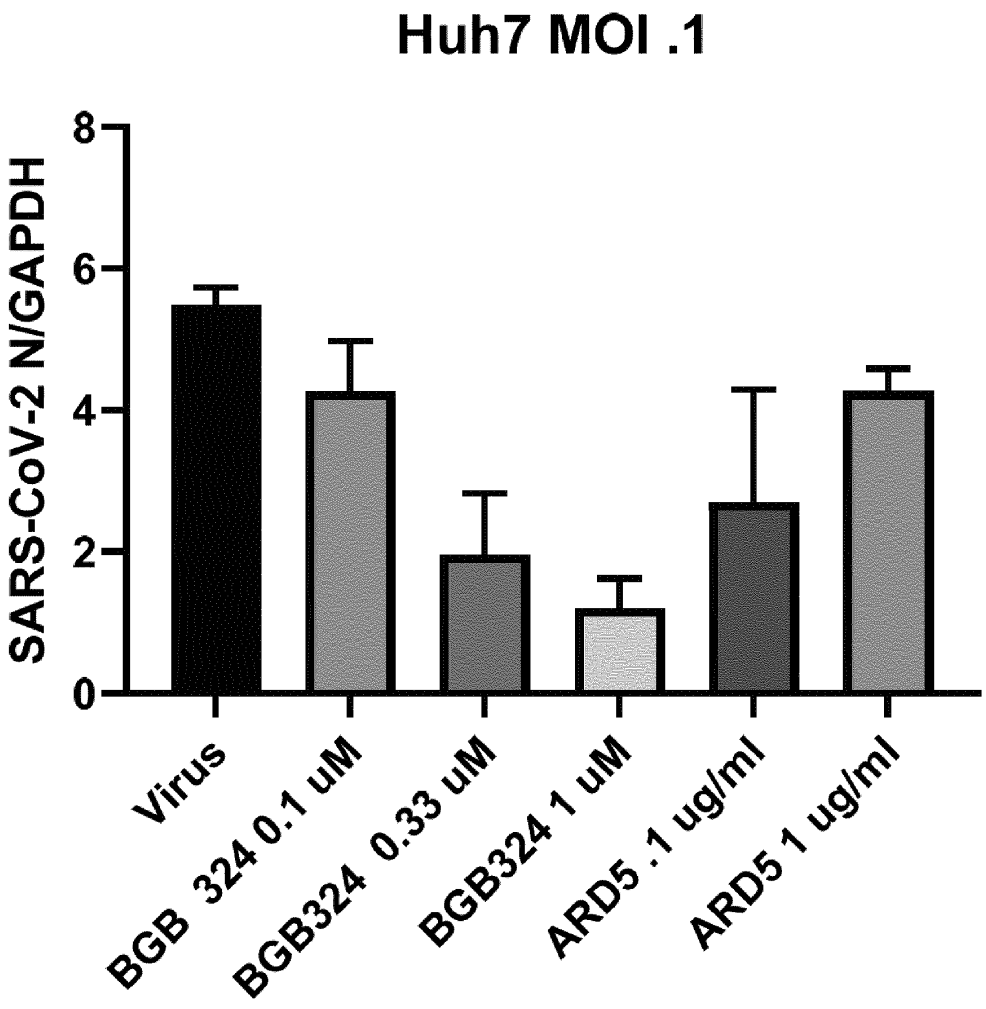

Huh7 MOI .1
SARS-CoV-2 N/GAPDH
8
6
4
2
0
Virus
BGB 324 0.1 uM
BGB324 0.33 uM
BGB324 1 uM
ARD5 .1 ug/ml
ARD5 1 ug/ml

Figure 14

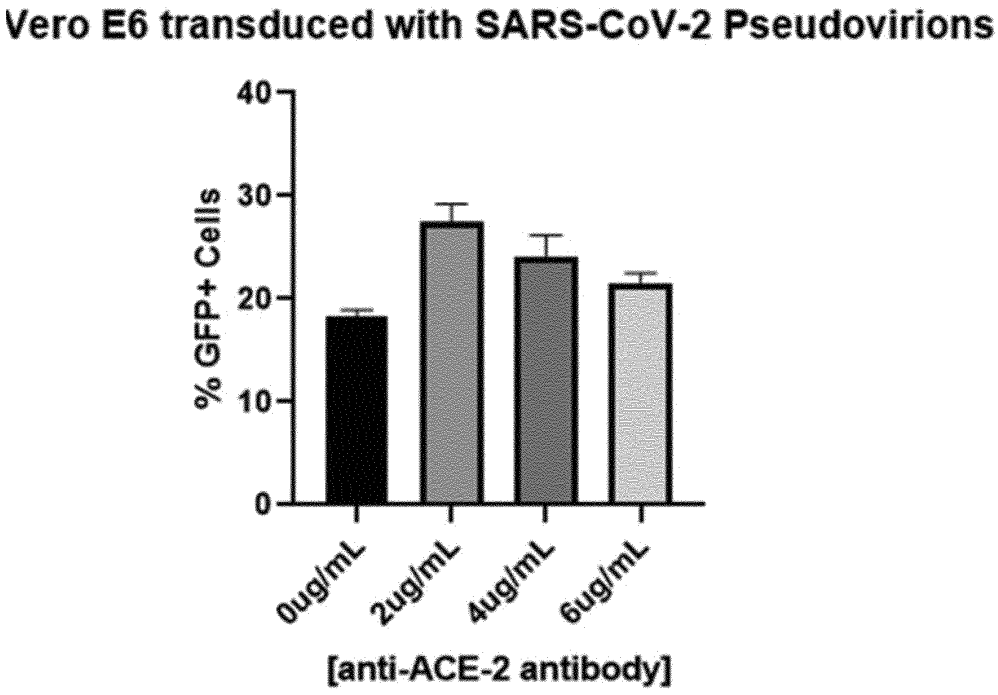

Vero E6 transduced with SARS-CoV-2 Pseudovirions
% GFP+ Cells
40
30
20
10
0
0ug/mL
2ug/mL
4ug/mL
6ug/mL
[anti-ACE-2 antibody]

Figure 15

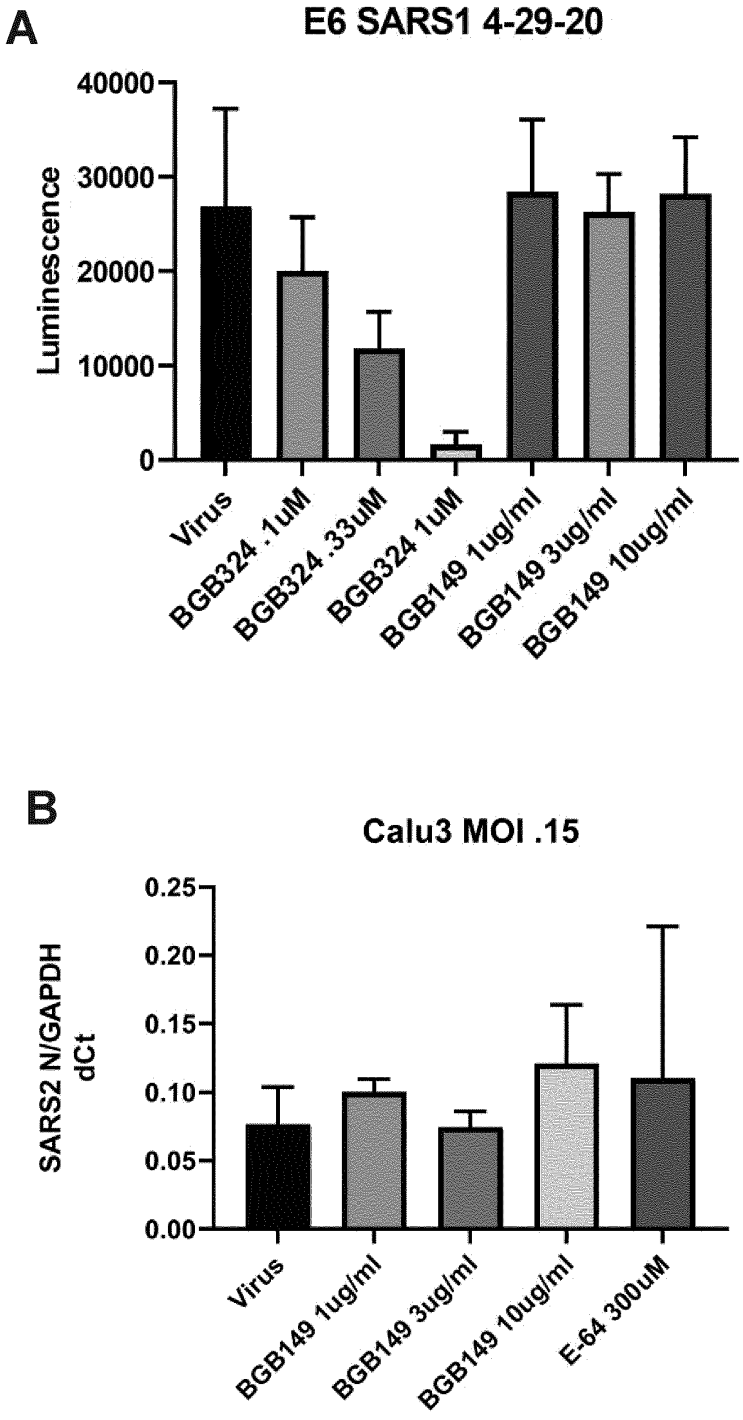

A
E6 SARS1 4-29-20
Luminescence
40000
30000
20000
10000
0
Virus
BGB324 .1uM
BGB324 .33uM
BGB324 1uM
BGB149 1ug/ml
BGB149 3ug/ml
BGB149 10ug/ml
B
Calu3 MOI .15
SARS2 N/GAPDH dCt
0.25
0.20
0.15
0.10
0.05
0.00
Virus
BGB149 1ug/ml
BGB149 3ug/ml
BGB149 10ug/ml
E-64 300uM

Figure 16

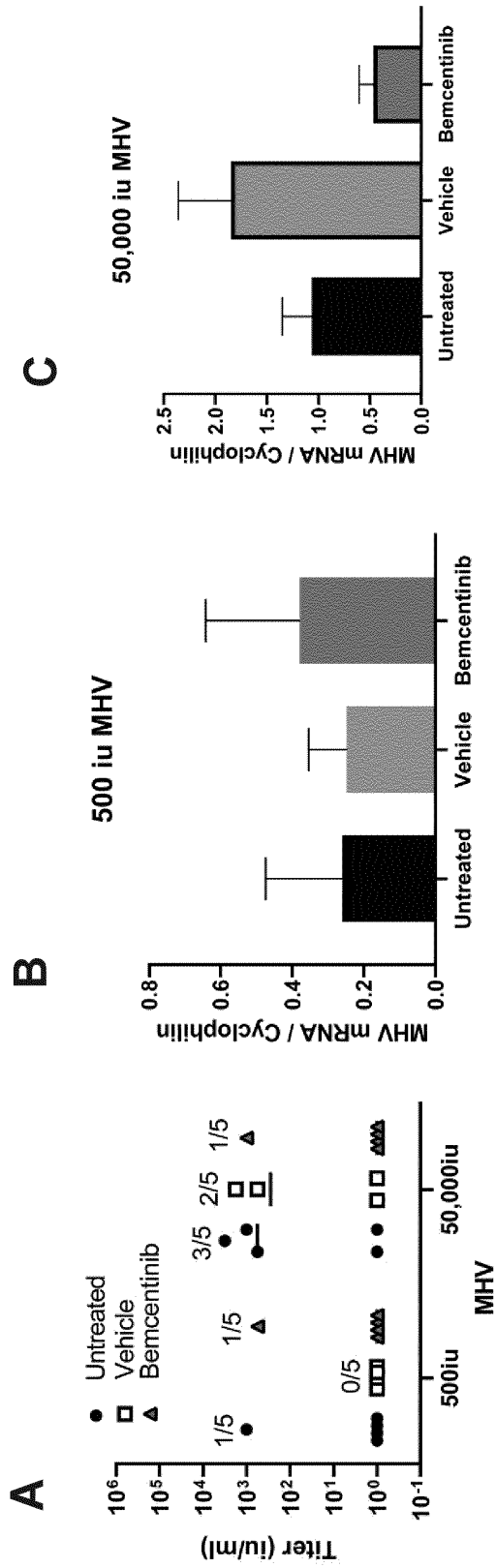

A
Titer (iu/ml)
Untreated
Vehicle
Bemcentinib
1/5
1/5
0/5
3/5
2/5
1/5
500iu
50,000iu
MHV
B
500 iu MHV
MHV mRNA / Cyclophilin
Untreated
Vehicle
Bemcentinib
C
50,000 iu MHV
MHV mRNA / Cyclophilin
Untreated
Vehicle
Bemcentinib

Figure 17

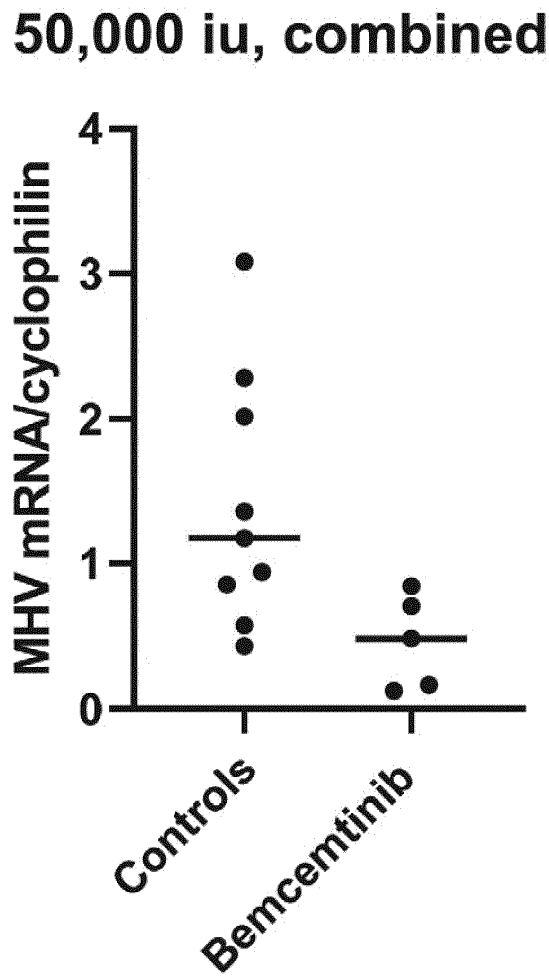

MHV 50,000 iu, combined controls
MHV mRNA/cyclophilin
4
3
2
1
0
Controls
Bemcemtinib

Figure 18

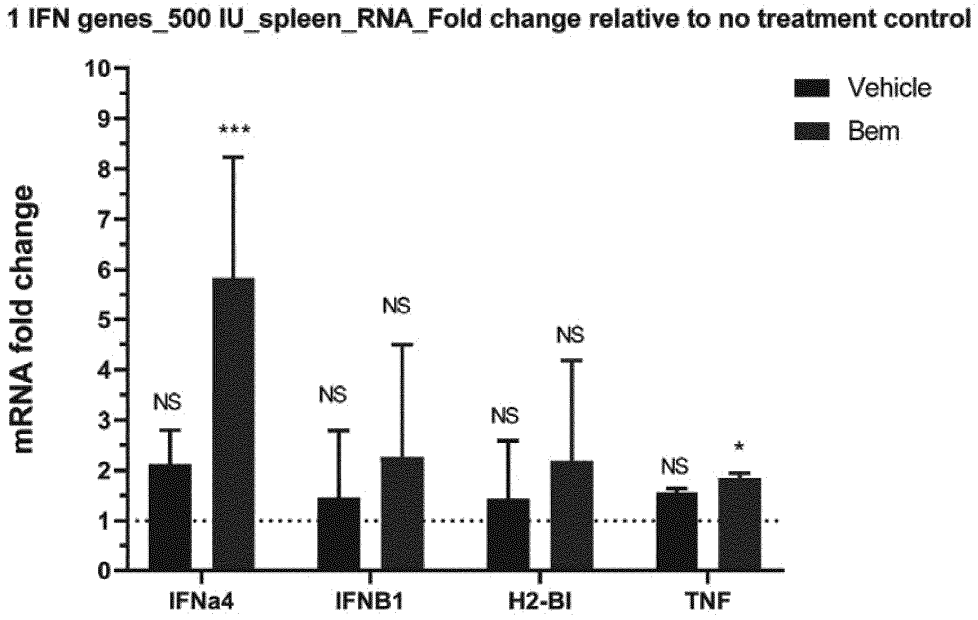

Type 1 IFN genes_500 IU_spleen_RNA_Fold change relative to no treatment control
mRNA fold change
Vehicle
Bem
NS
***
NS
NS
NS
NS
NS
*
IFNa4
IFNB1
H2-BI
TNF

Figure 19

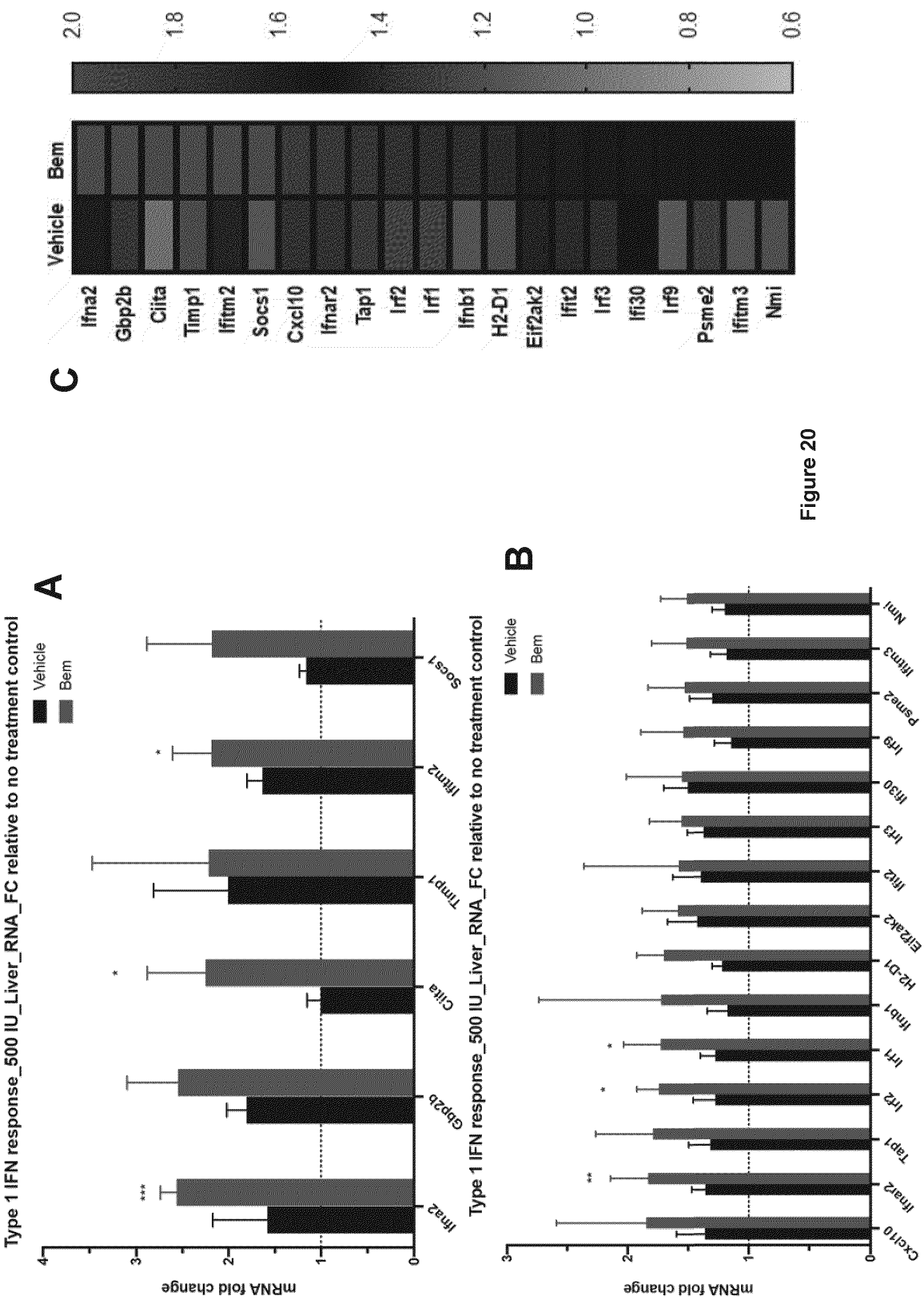

A
Type 1 IFN response_500 IU_Liver_RNA_FC relative to no treatment control
Vehicle
Bem
mRNA fold change
Ifna2
Gbp2b
Ciita
Timp1
Ifitm2
Socs1
B
Type 1 IFN response_500 IU_Liver_RNA_FC relative to no treatment control
Vehicle
Bem
mRNA fold change
Cxcl10
Ifnar2
Tap1
Irf2
Irf1
Ifnb1
H2-D1
Eif2ak2
Ifit2
Irf3
Ifi30
Irf9
Psme2
Ifitm3
Nmi
C
Vehicle
Bem
Ifna2
Gbp2b
Ciita
Timp1
Ifitm2
Socs1
Cxcl10
Ifnar2
Tap1
Irf2
Irf1
Ifnb1
H2-D1
Eif2ak2
Ifit2
Irf3
Ifi30
Irf9
Psme2
Ifitm3
Nmi
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6

Figure 20

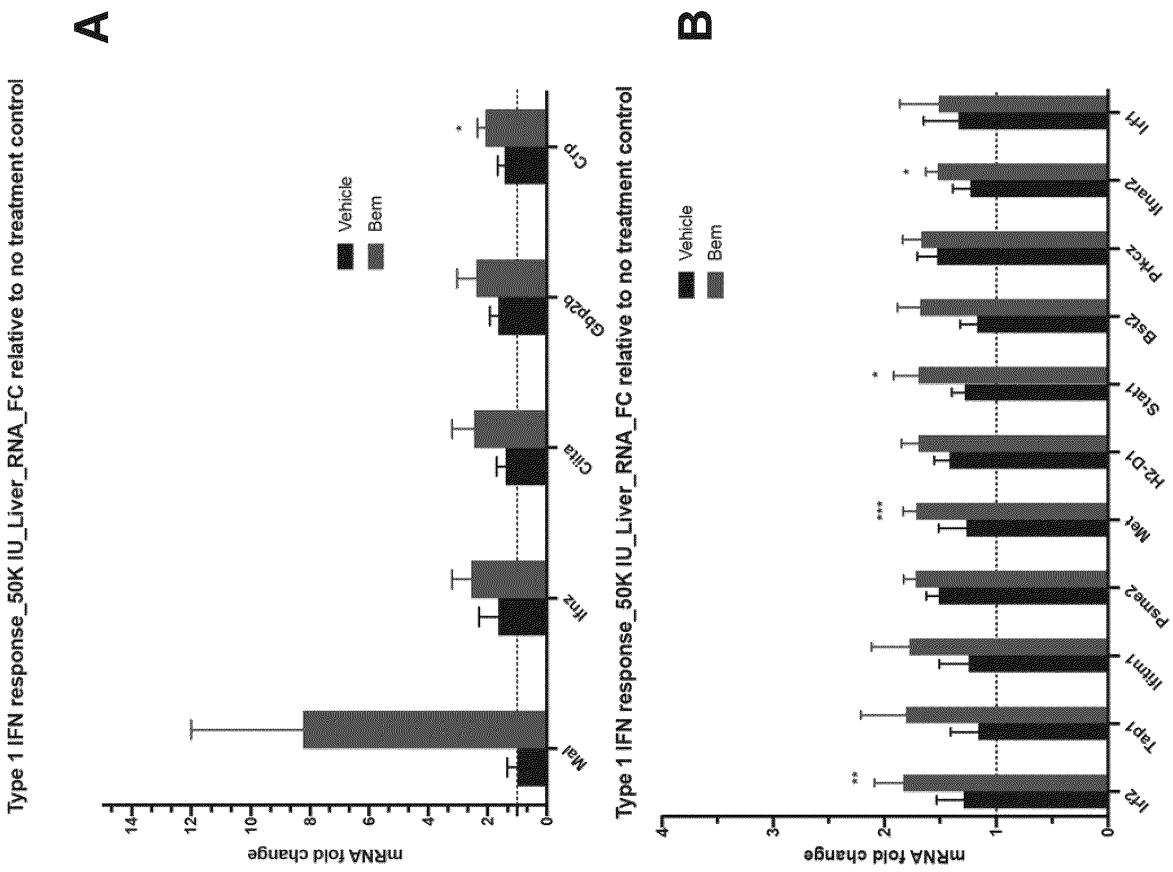

A
Type 1 IFN response_50K IU_Liver_RNA_FC relative to no treatment control
mRNA fold change
Vehicle
Bem
Mal
Ifnz
Ciita
Gbp2b
Crp
B
Type 1 IFN response_50K IU_Liver_RNA_FC relative to no treatment control
mRNA fold change
Irf2
Tap1
Ifitm1
Psme2
Met
H2-D1
Stat1
Bst2
Prkcz
Ifnar2
Irf1
C
Vehicle
Bem
Mal
Ifnz
Ciita
Gbp2b
Crp
Irf2
Tap1
Ifitm1
Psme2
Met
H2-D1
Stat1
Bst2
Prkcz
Ifnar2
Irf1

Figure 21

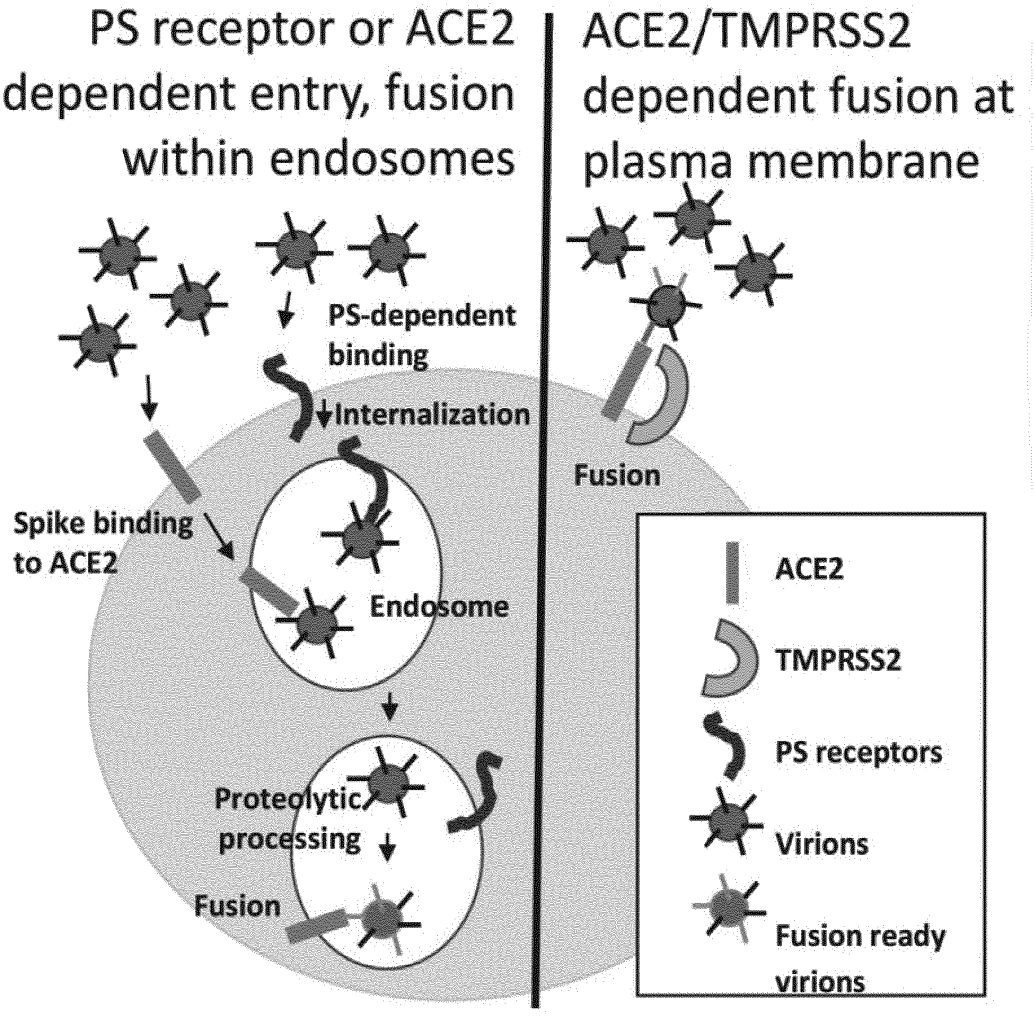

PS receptor or ACE2 dependent entry, fusion within endosomes
ACE2/TMPRSS2 dependent fusion at plasma membrane
PS-dependent binding
Internalization
Spike binding to ACE2
Endosome
Proteolytic processing
Fusion
Fusion
ACE2
TMPRSS2
PS receptors
Virions
Fusion ready virions

Figure 22

| | Setting | Severity | Supportive intervention | BGBC020 | Dexa-methasone | IL-6 receptor antagonists | Remdesivir |
|---|---|---|---|---|---|---|---|
| 0 | Uninfected | no clinical or virological evidence of infection | | | | | |
| 1 | Ambulatory | no limitation of activities | | | | | |
| 2 | | limitation of activities | | | | | |
| 3 | Hospitalised | mild | no oxygen therapy | except India | | | |
| 4 | | | oxygen by mask or nasal prongs | | | | |
| 5 | | severe | noninvasive ventilation or high-flow $O_2$ | | | | |
| 6 | | | intubation and mechanical ventilation | | | | |
| 7 | | | ventilation & additional organ support<br>- vasopressors<br>- renal replacement therapy (RRT)<br>- extracorporeal membrane oxygenation (ECMO) | | | | |
| 8 | | Death | | | | | |

Figure 23

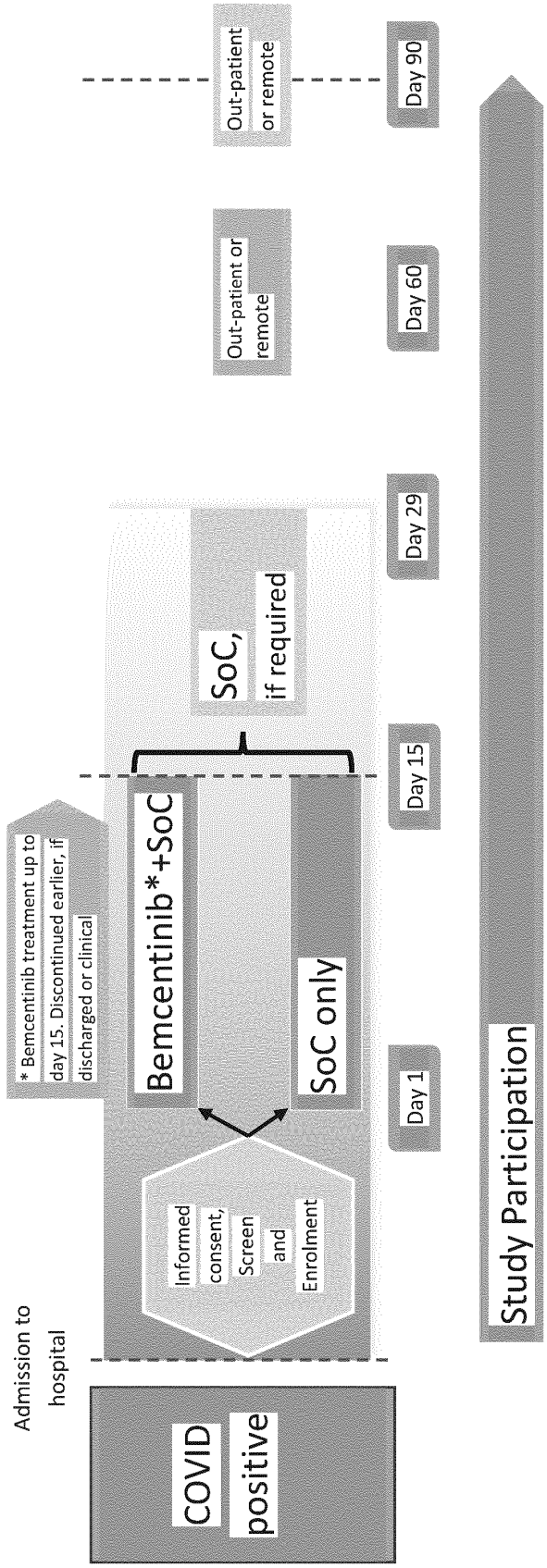

COVID positive
Admission to hospital
Informed consent, Screen and Enrolment
Bemcentinib*+SoC
SoC only
* Bemcentinib treatment up to day 15. Discontinued earlier, if discharged or clinical
SoC, if required
Day 1
Day 15
Day 29
Day 60
Day 90
Out-patient or remote
Out-patient or remote
Study Participation

Figure 24

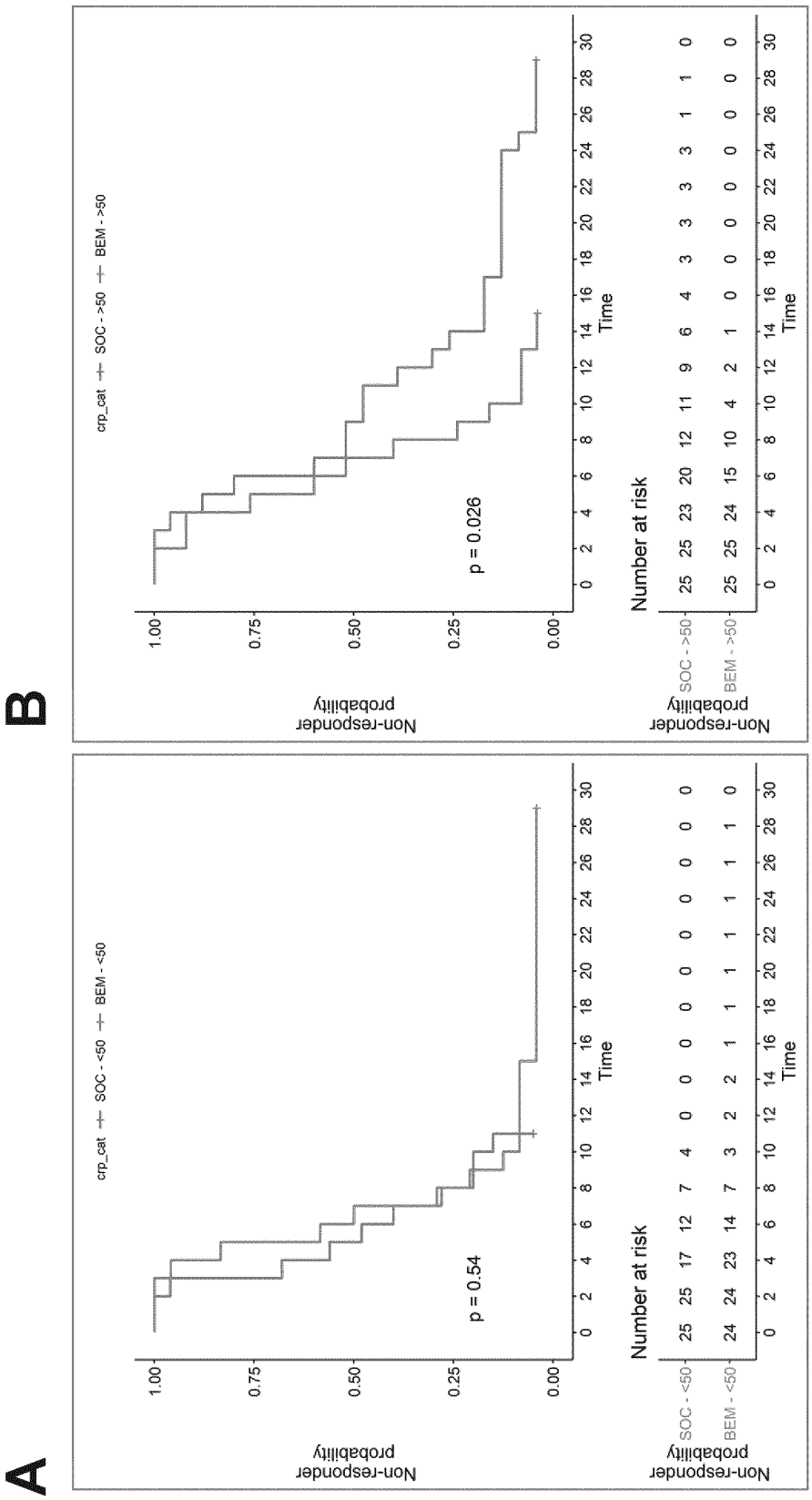

A
B
crp_cat SOC - <50 BEM - <50
crp_cat SOC - >50 BEM - >50
Non-responder probability
1.00
0.75
0.50
0.25
0.00
p = 0.54
p = 0.026
Time
Number at risk
SOC - <50
BEM - <50
SOC - >50
BEM - >50

Figure 25

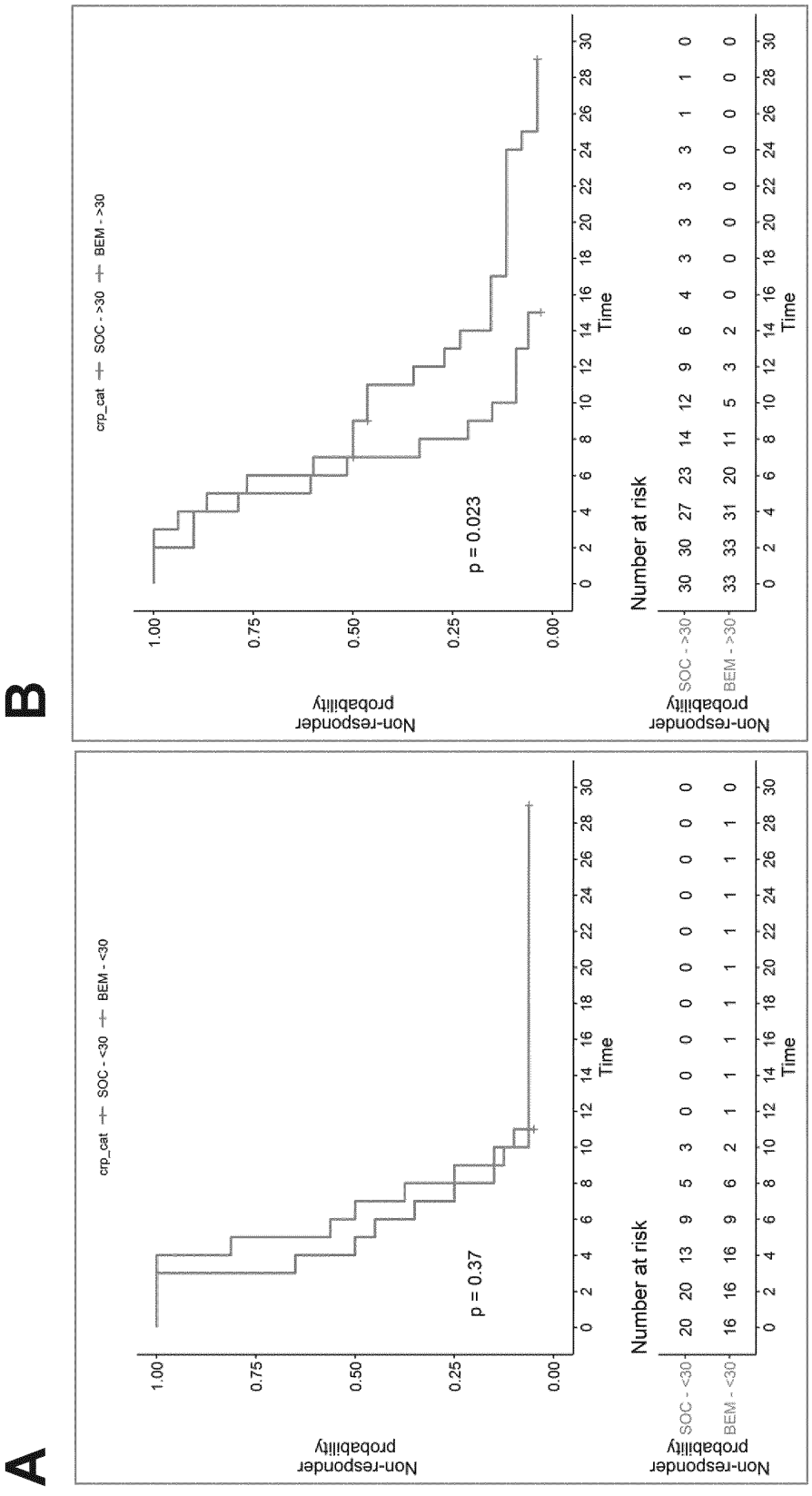

A
B
crp_cat SOC - <30 BEM - <30
SOC - >30 BEM - >30
Non-responder probability
Time
p = 0.37
p = 0.023
Number at risk
SOC - <30
BEM - <30
SOC - >30
BEM - >30

Figure 26

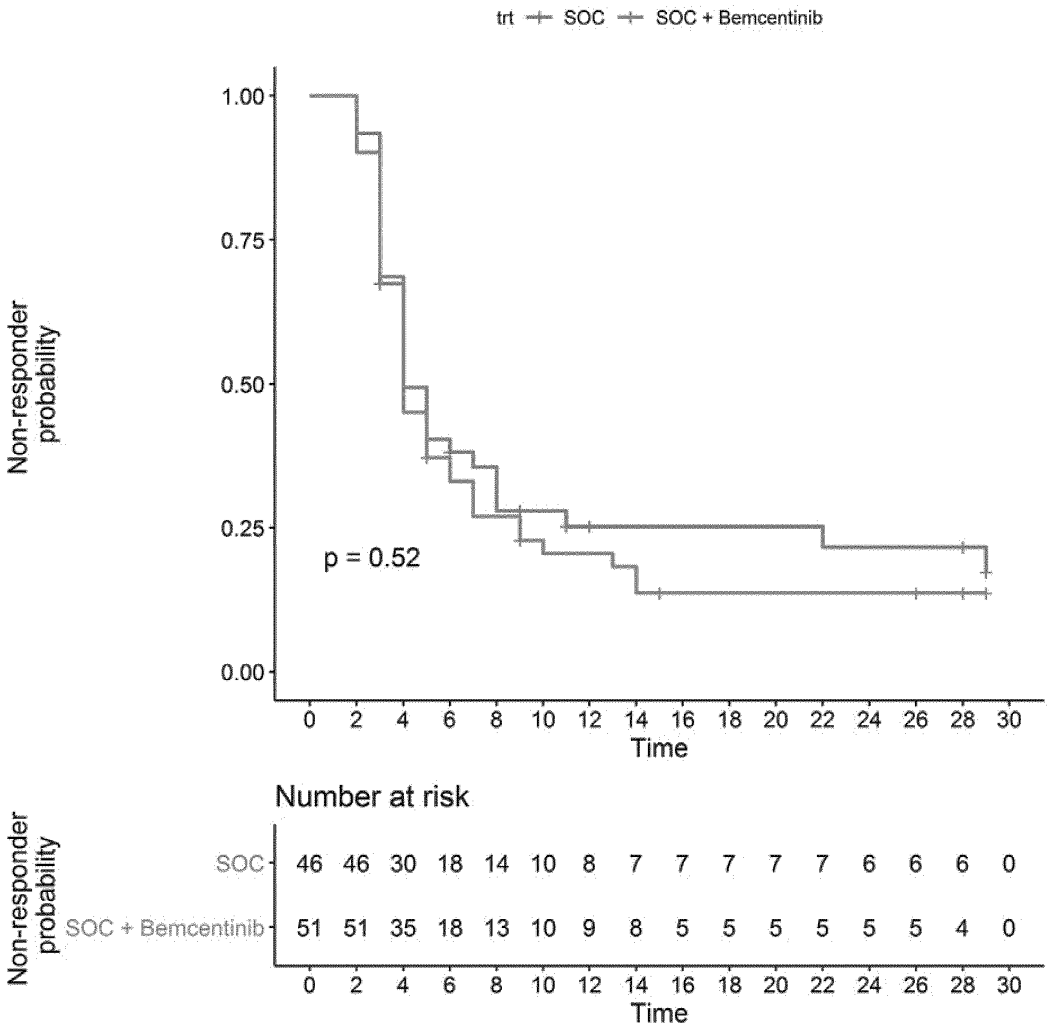

trt SOC SOC + Bemcentinib
Non-responder probability
1.00
0.75
0.50
0.25
0.00
p = 0.52
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time
Number at risk
SOC 46 46 30 18 14 10 8 7 7 7 7 7 6 6 6 0
SOC + Bemcentinib 51 51 35 18 13 10 9 8 5 5 5 5 5 5 4 0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time

Figure 27

Figure 28

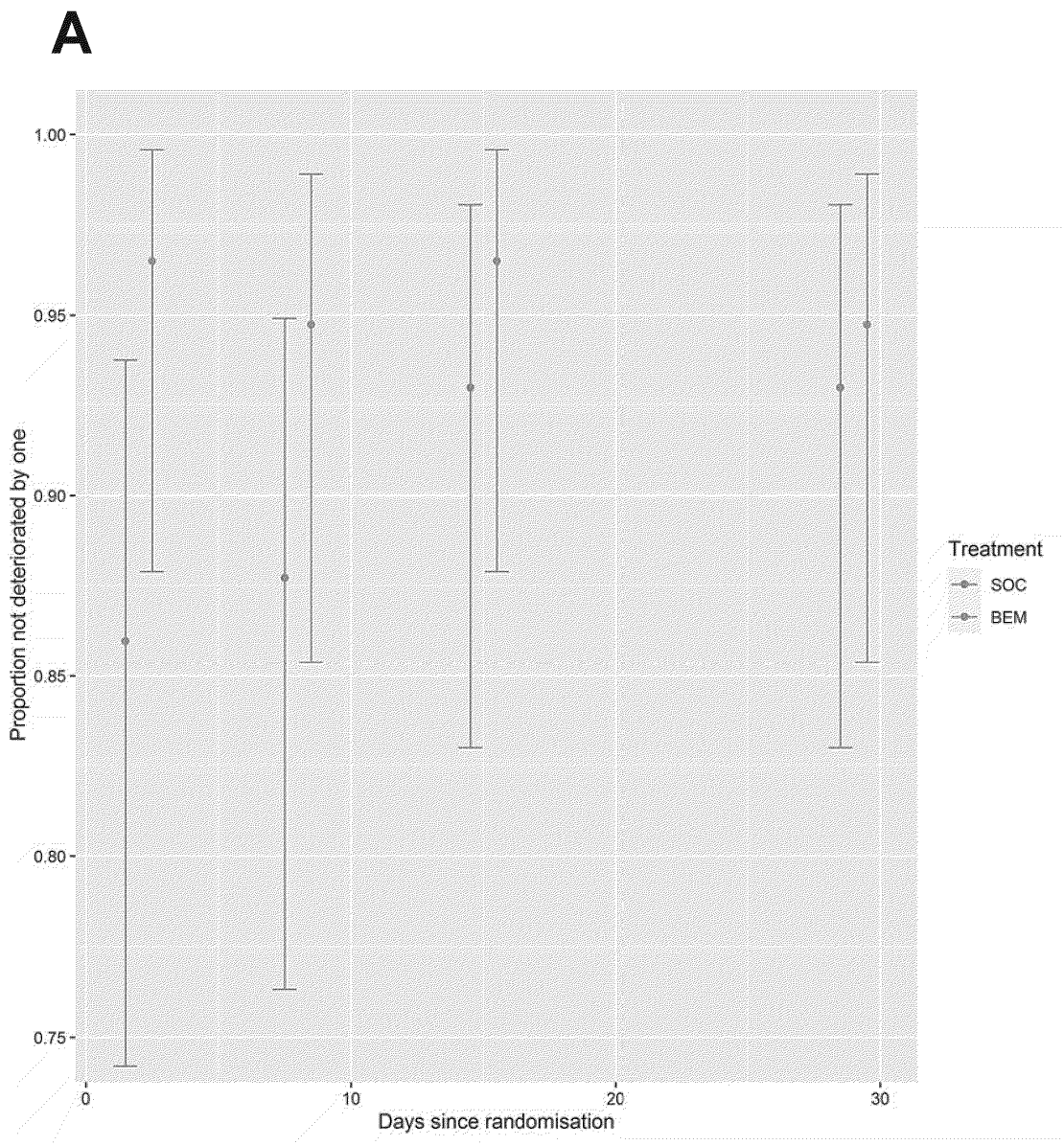

A
1.00
0.95
0.90
0.85
0.80
0.75
Proportion not deteriorated by one
0
10
20
30
Days since randomisation
Treatment
SOC
BEM

**Figure 28 Continued**

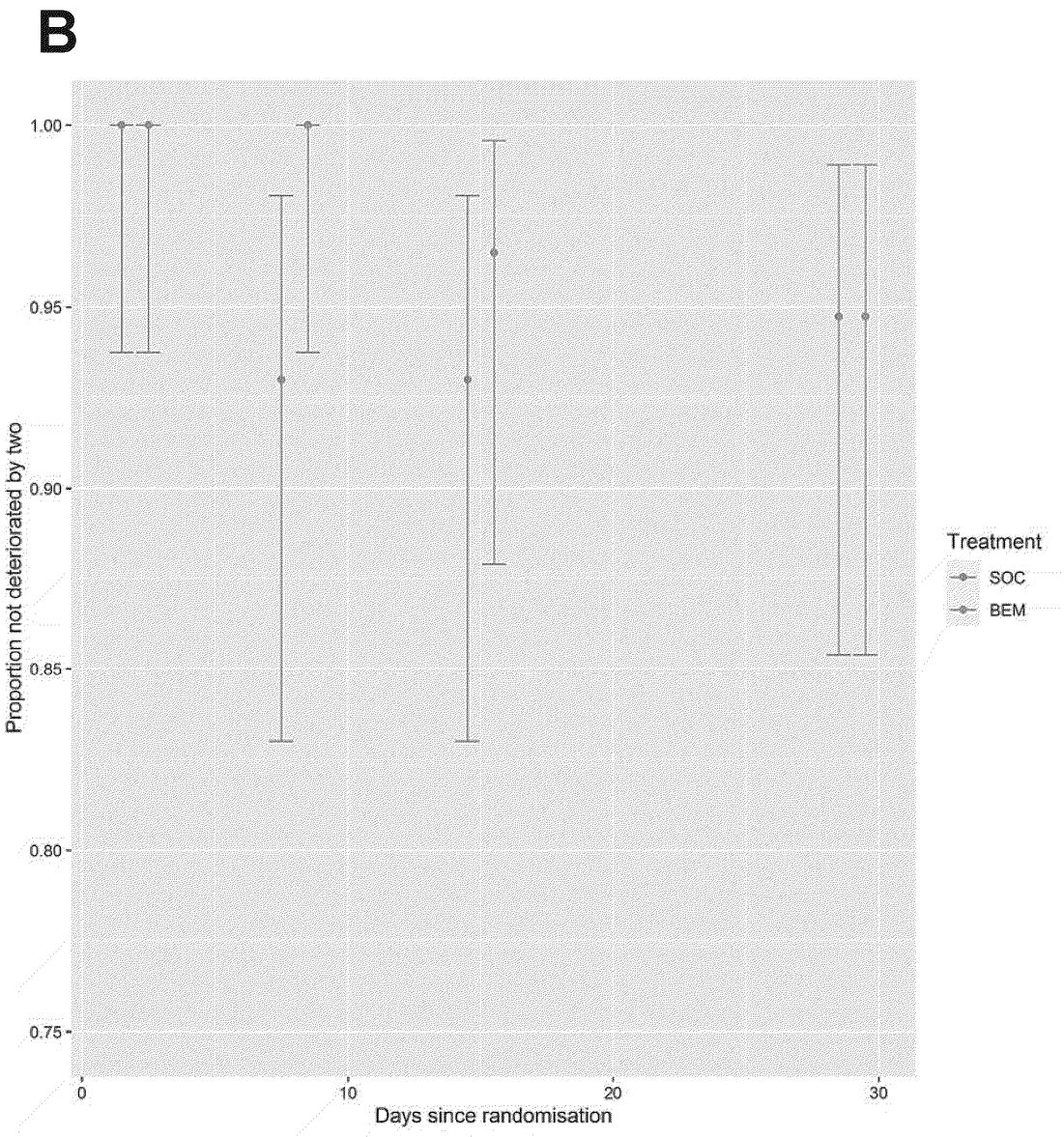


**Figure 28 Continued**

C

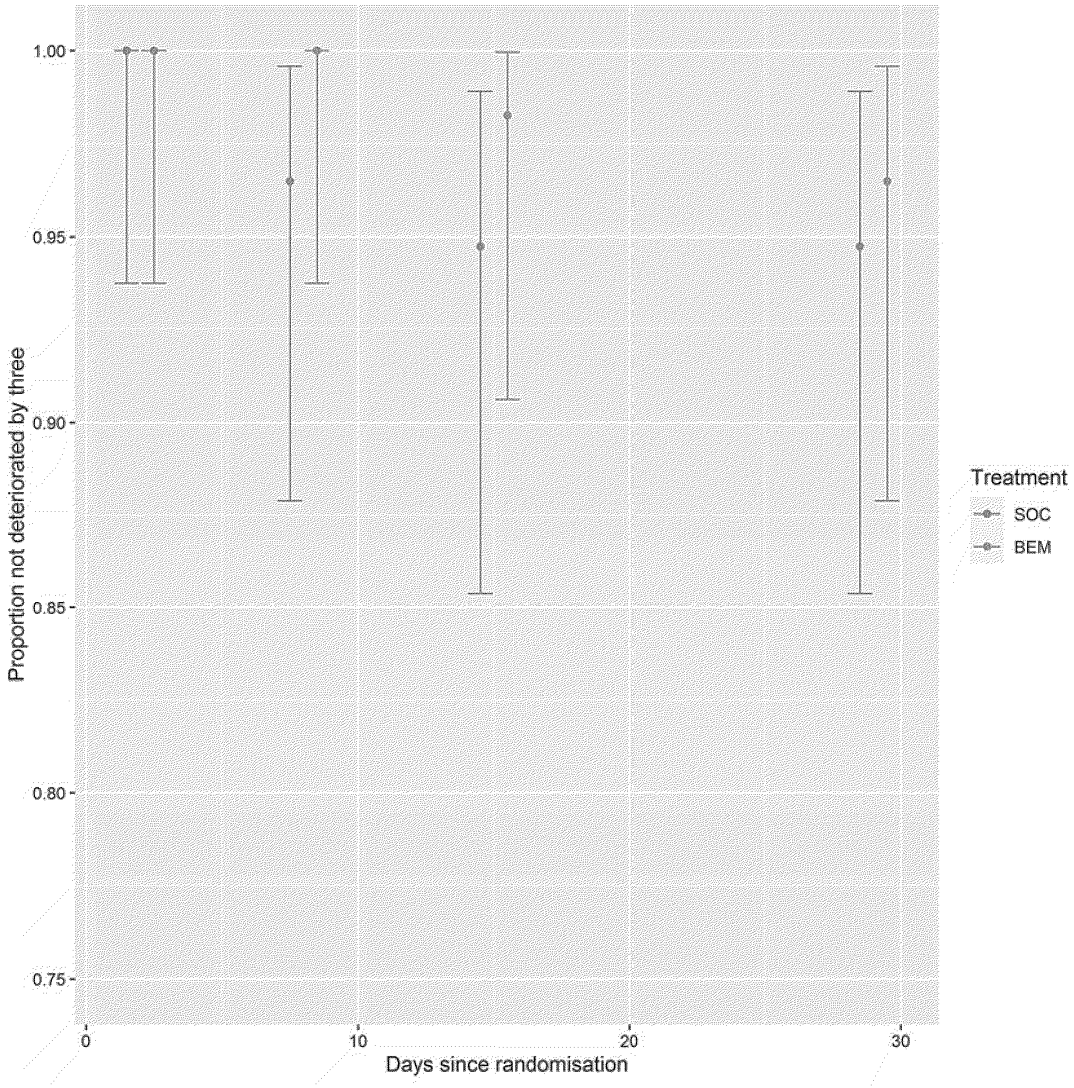


Figure 29

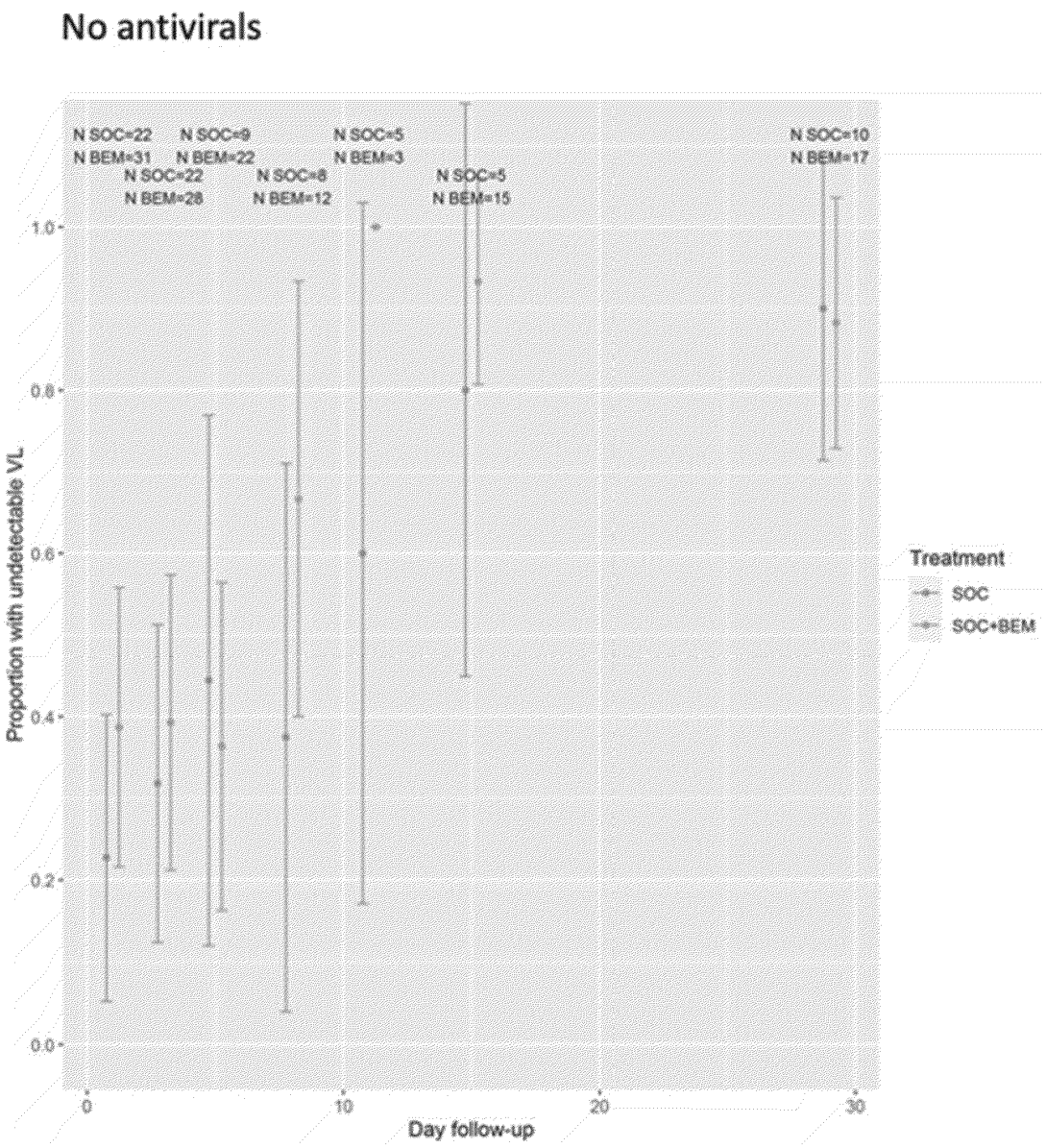

No antivirals
N SOC=22
N BEM=31
N SOC=9
N BEM=22
N SOC=5
N BEM=3
N SOC=22
N BEM=28
N SOC=8
N BEM=12
N SOC=5
N BEM=15
N SOC=10
N BEM=17
Proportion with undetectable VL
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
Day follow-up
Treatment
SOC
SOC+BEM

Figure 29 Continued

