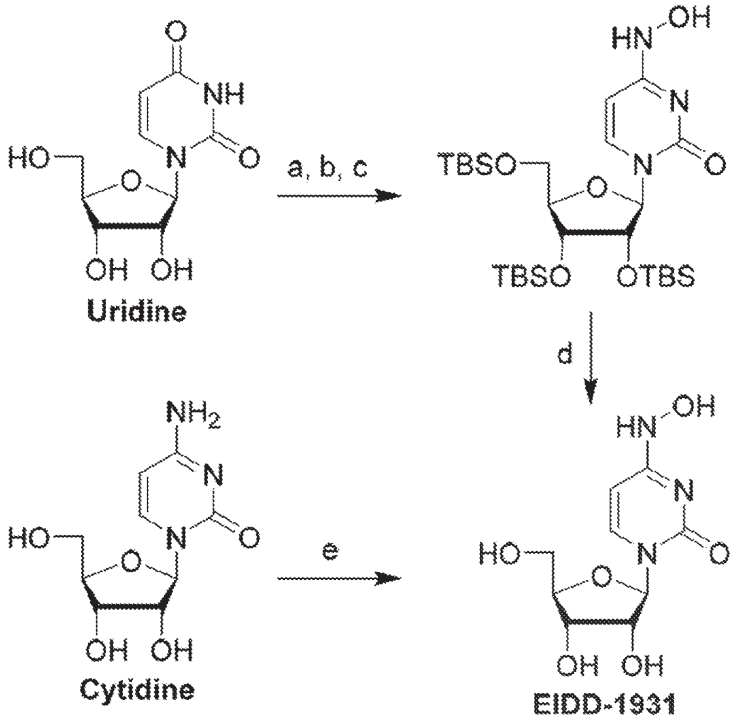

Uridine
a, b, c
TBSO
TBSO
OTBS
d
Cytidine
e
EIDD-1931

FIG. 1

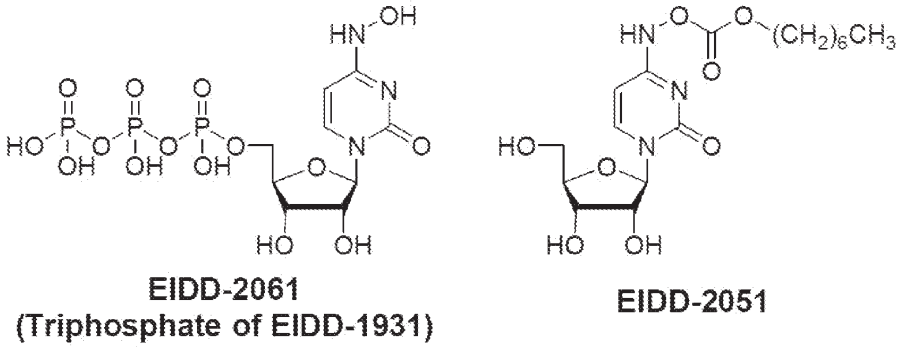
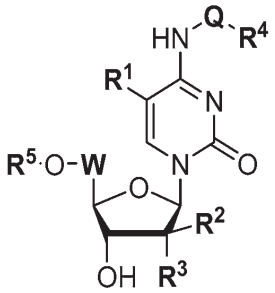

EIDD-2061
(Triphosphate of EIDD-1931)
EIDD-2051

FIG. 2



W = CH_2, CF_2, CD_2

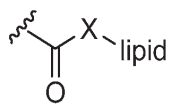
Q = O, NH

R^1 = H, F, Cl, Br, I, CH_3, CF_3, SMe, D, alkyl, alkenyl, allenyl, alkynyl

R^2 = H, OH, CH_3, alkyl, alkenyl, allenyl, alkynyl

R^3 = OH, H, F, Cl

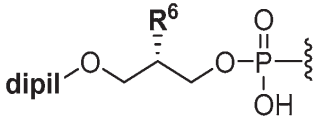
R^4, **R**^{5} = H,



where X = CH_2, O, S, or NH, and

lipid = *n*-C_6H_{13} through $C_{16}H_{33}$

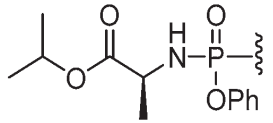
phospholipid,



where **R**^{6} = H or OBn, and

lipid = *n*-C_6H_{13} through $C_{16}H_{33}$

phosphoramidate,



cycloSal phosphotriester

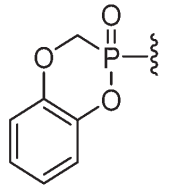


FIG. 3

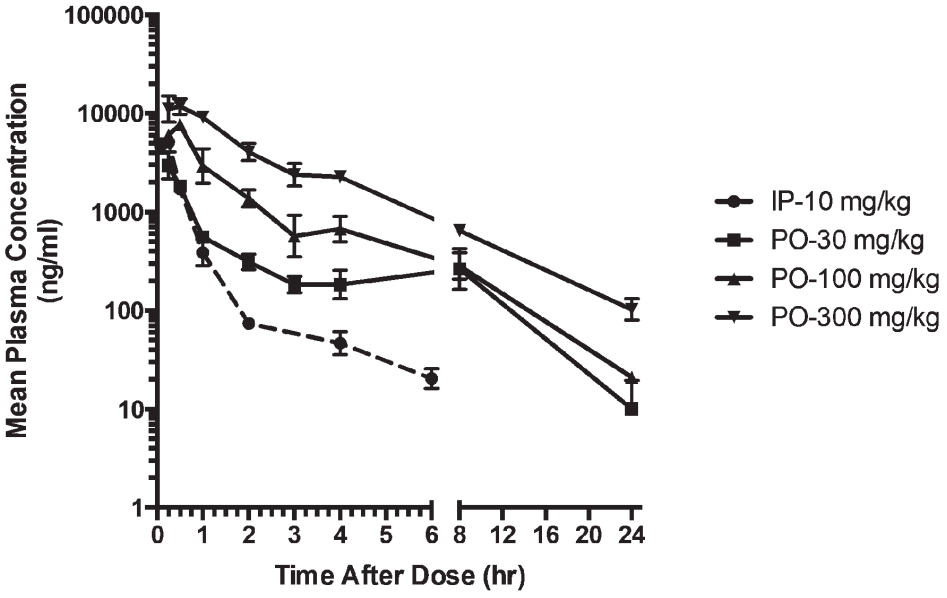

Mean Plasma Concentration (ng/ml)
100000
10000
1000
100
10
1
0 1 2 3 4 5 6 8 12 16 20 24
Time After Dose (hr)
IP-10 mg/kg
PO-30 mg/kg
PO-100 mg/kg
PO-300 mg/kg

FIG. 4

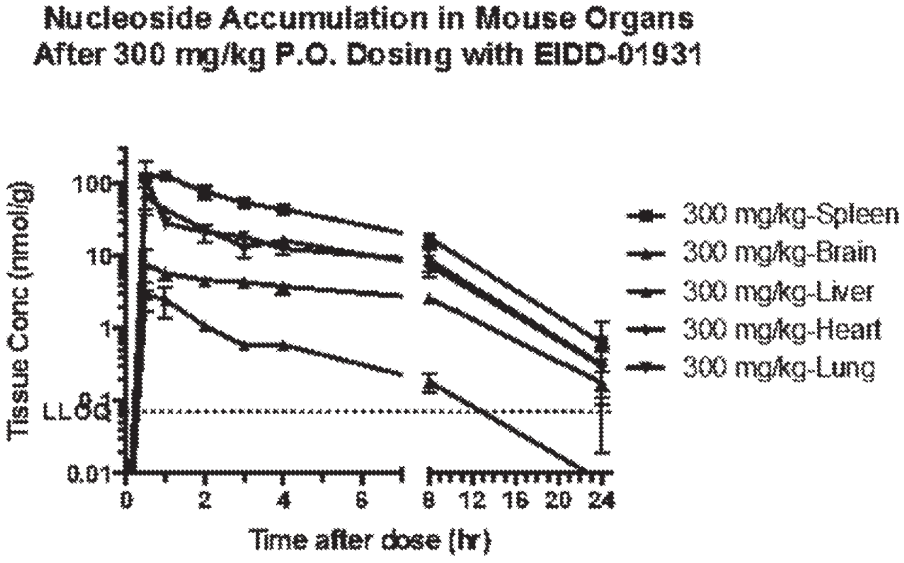

Nucleoside Accumulation in Mouse Organs
After 300 mg/kg P.O. Dosing with EIDD-01931
Tissue Conc (nmol/g)
100
10
1
LLOQ
0.01
0 2 4 6 8 12 16 20 24
Time after dose (hr)
300 mg/kg-Spleen
300 mg/kg-Brain
300 mg/kg-Liver
300 mg/kg-Heart
300 mg/kg-Lung

FIG. 5

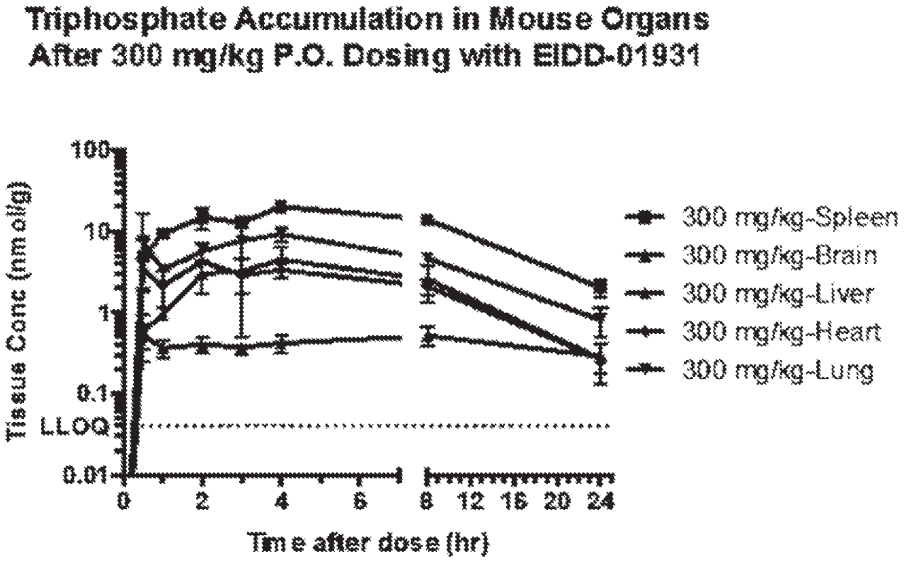

Triphosphate Accumulation in Mouse Organs
After 300 mg/kg P.O. Dosing with EIDD-01931
Tissue Conc (nmol/g)
100
10
1
0.1
LLOQ
0.01
0
2
4
6
8
12
16
20
24
Time after dose (hr)
300 mg/kg-Spleen
300 mg/kg-Brain
300 mg/kg-Liver
300 mg/kg-Heart
300 mg/kg-Lung

FIG. 6

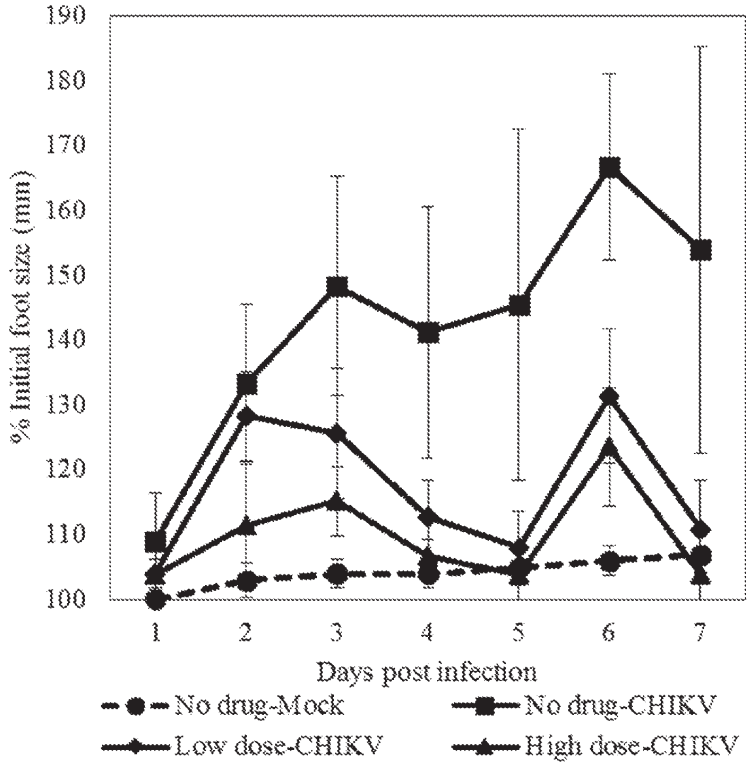

190
180
170
160
150
140
130
120
110
100
% Initial foot size (mm)
1
2
3
4
5
6
7
Days post infection
No drug-Mock
No drug-CHIKV
Low dose-CHIKV
High dose-CHIKV

FIG. 7

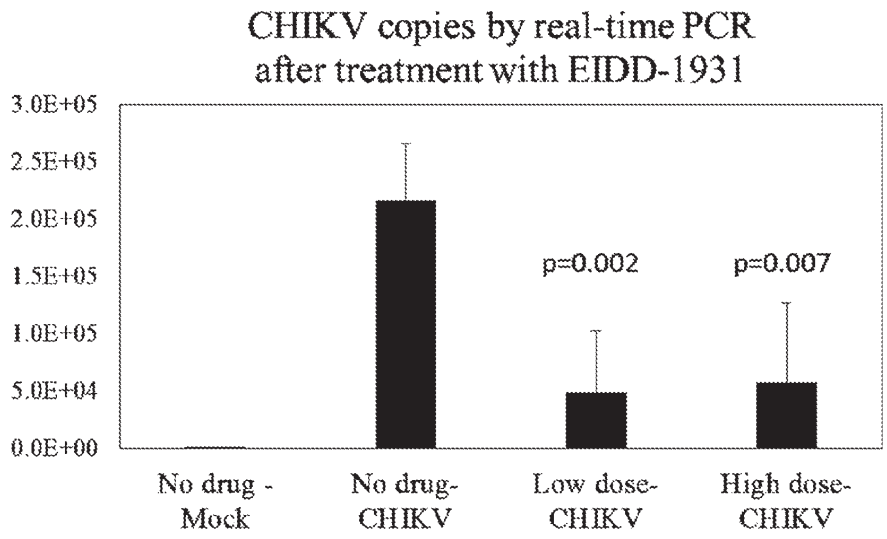

CHIKV copies by real-time PCR
after treatment with EIDD-1931
3.0E+05
2.5E+05
2.0E+05
1.5E+05
1.0E+05
5.0E+04
0.0E+00
p=0.002
p=0.007
No drug - Mock
No drug- CHIKV
Low dose- CHIKV
High dose- CHIKV

FIG. 8

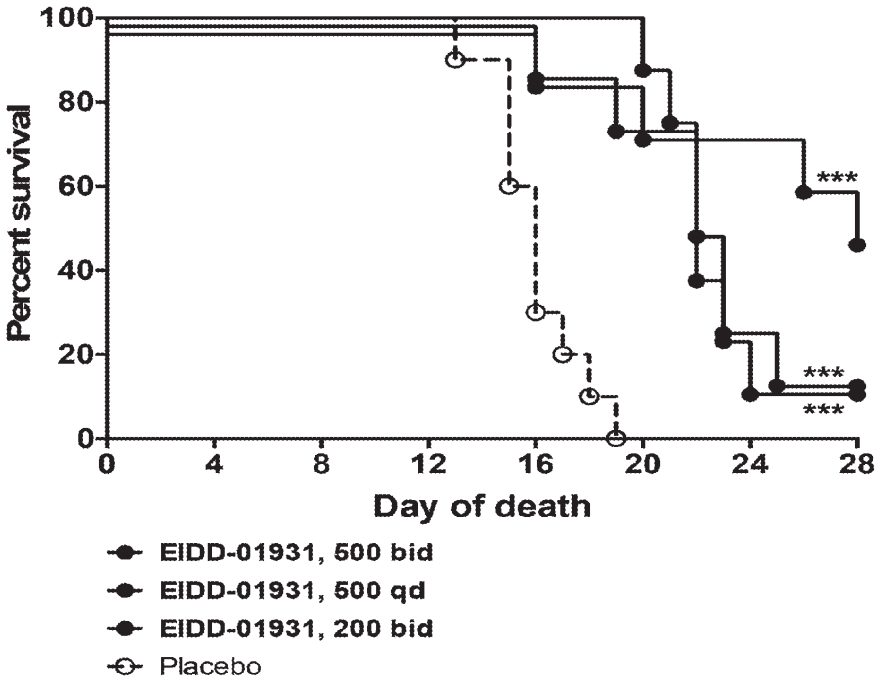

Percent survival
100
80
60
40
20
0
0
4
8
12
16
20
24
28
Day of death
***
***
***
EIDD-01931, 500 bid
EIDD-01931, 500 qd
EIDD-01931, 200 bid
Placebo

FIG. 9

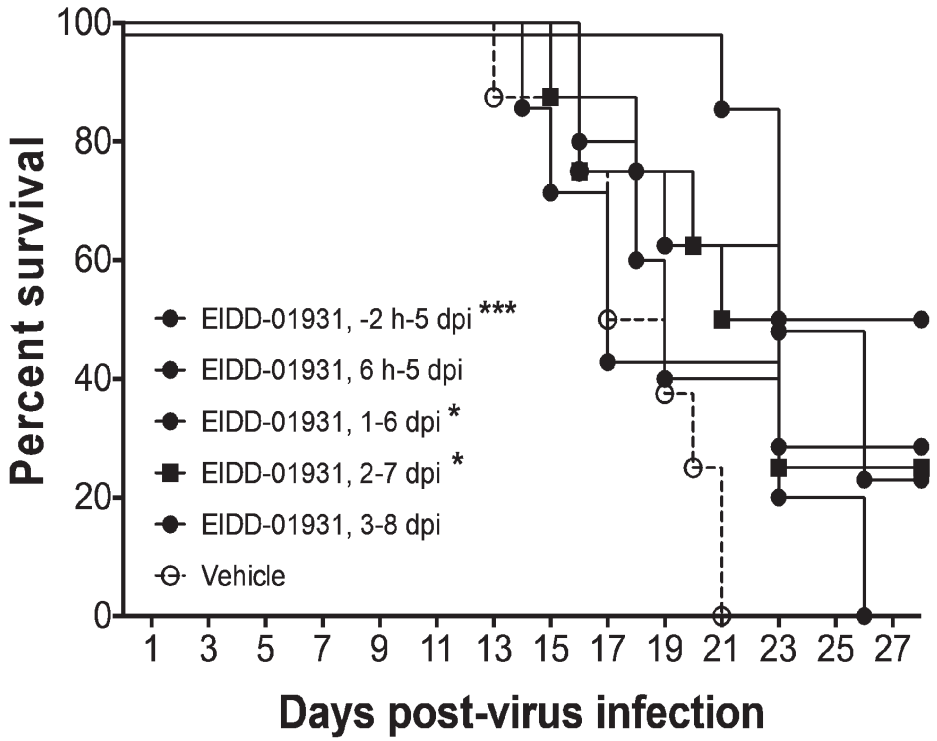

Percent survival
100
80
60
40
20
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27
Days post-virus infection
EIDD-01931, -2 h-5 dpi ***
EIDD-01931, 6 h-5 dpi
EIDD-01931, 1-6 dpi *
EIDD-01931, 2-7 dpi *
EIDD-01931, 3-8 dpi
Vehicle

FIG. 10

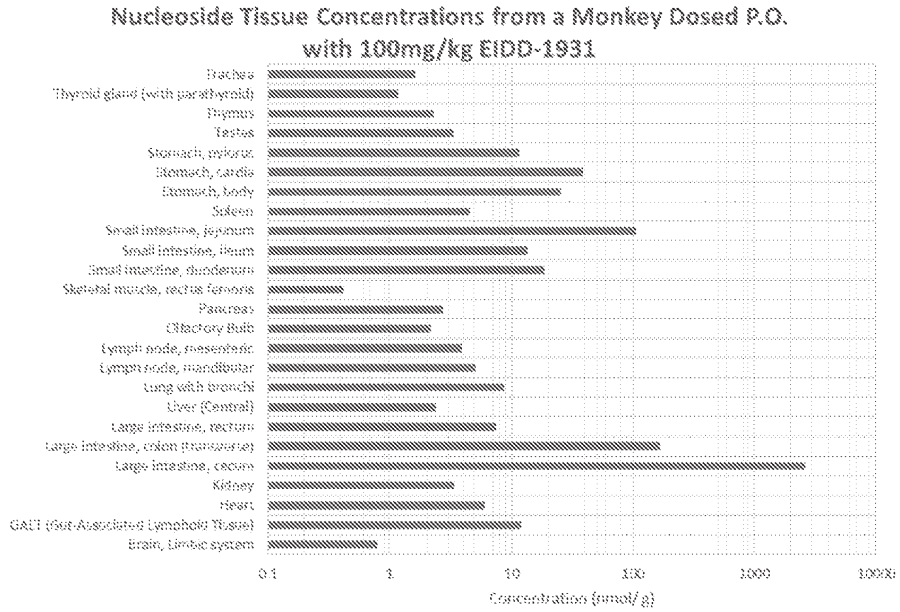

Nucleoside Tissue Concentrations from a Monkey Dosed P.O. with 100mg/kg EIDD-1931
Trachea
Thyroid gland (with parathyroid)
Thymus
Testes
Stomach, pylorus
Stomach, cardia
Stomach, body
Spleen
Small intestine, jejunum
Small intestine, ileum
Small intestine, duodenum
Skeletal muscle, rectus femoris
Pancreas
Olfactory Bulb
Lymph node, mesenteric
Lymph node, mandibular
Lung with bronchi
Liver (Central)
Large intestine, rectum
Large intestine, colon (transverse)
Large intestine, cecum
Kidney
Heart
GALT (Gut-Associated Lymphoid Tissue)
Brain, Limbic system
0.1
1
10
100
1000
10000
Concentration (nmol/ g)

FIG. 11

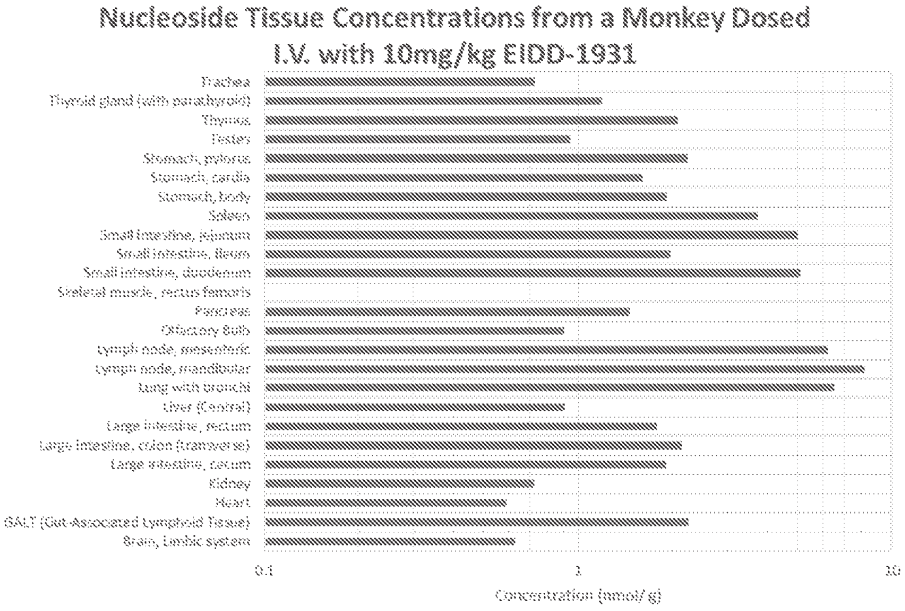

Nucleoside Tissue Concentrations from a Monkey Dosed I.V. with 10mg/kg EIDD-1931
Trachea
Thyroid gland (with parathyroid)
Thymus
Testes
Stomach, pylorus
Stomach, cardia
Stomach, body
Spleen
Small intestine, jejunum
Small intestine, ileum
Small intestine, duodenum
Skeletal muscle, rectus femoris
Pancreas
Olfactory Bulb
Lymph node, mesenteric
Lymph node, mandibular
Lung with bronchi
Liver (Central)
Large intestine, rectum
Large intestine, colon (transverse)
Large intestine, cecum
Kidney
Heart
GALT (Gut-Associated Lymphoid Tissue)
Brain, Limbic system
0.1
1
10
Concentration (nmol/ g)

FIG. 12

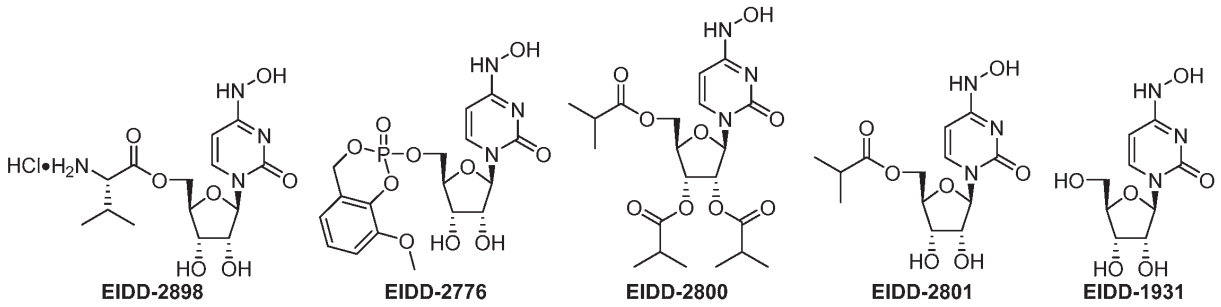


FIG. 13

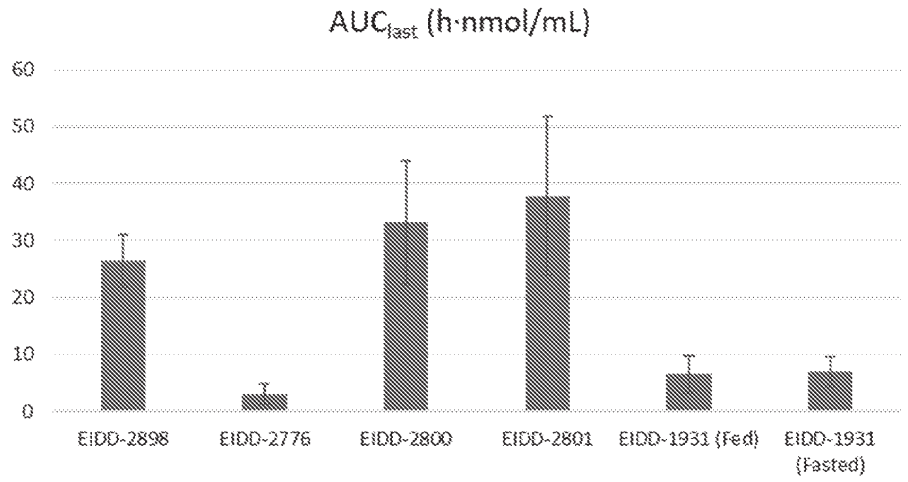

AUC$_{last}$ (h·nmol/mL)
60
50
40
30
20
10
0
EIDD-2898
EIDD-2776
EIDD-2800
EIDD-2801
EIDD-1931 (Fed)
EIDD-1931 (Fasted)

FIG. 14

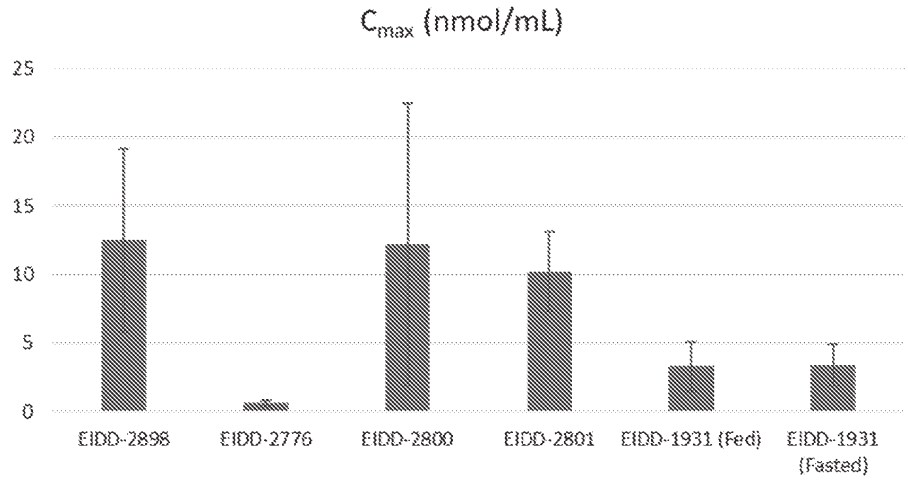

C_{max} (nmol/mL)
25
20
15
10
5
0
EIDD-2898
EIDD-2776
EIDD-2800
EIDD-2801
EIDD-1931 (Fed)
EIDD-1931 (Fasted)

FIG. 15

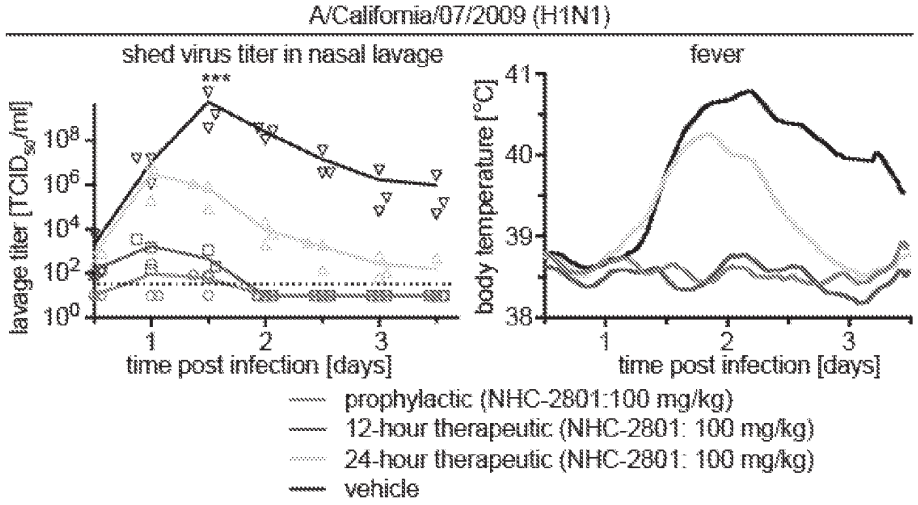

A/California/07/2009 (H1N1)
shed virus titer in nasal lavage
fever
lavage titer [TCID50/ml]
body temperature [°C]
time post infection [days]
time post infection [days]
prophylactic (NHC-2801:100 mg/kg)
12-hour therapeutic (NHC-2801: 100 mg/kg)
24-hour therapeutic (NHC-2801: 100 mg/kg)
vehicle

FIG. 16

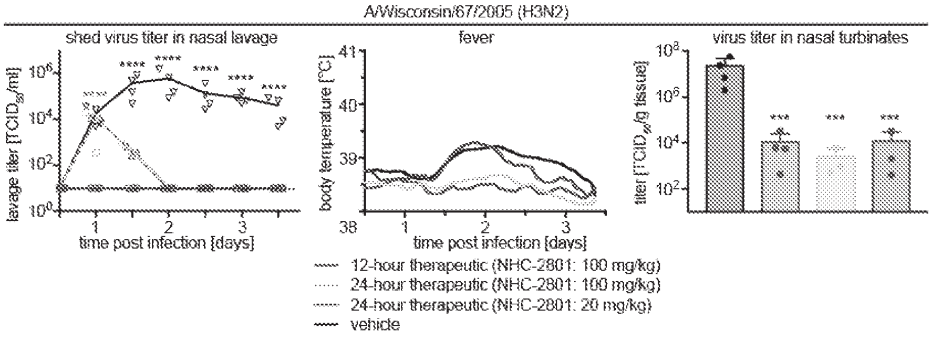

A/Wisconsin/67/2005 (H3N2)
shed virus titer in nasal lavage
fever
virus titer in nasal turbinates
lavage titer [TCID50/ml]
body temperature [°C]
titer [TCID50/g tissue]
time post infection [days]
time post infection [days]
12-hour therapeutic (NHC-2801: 100 mg/kg)
24-hour therapeutic (NHC-2801: 100 mg/kg)
24-hour therapeutic (NHC-2801: 20 mg/kg)
vehicle

FIG. 17

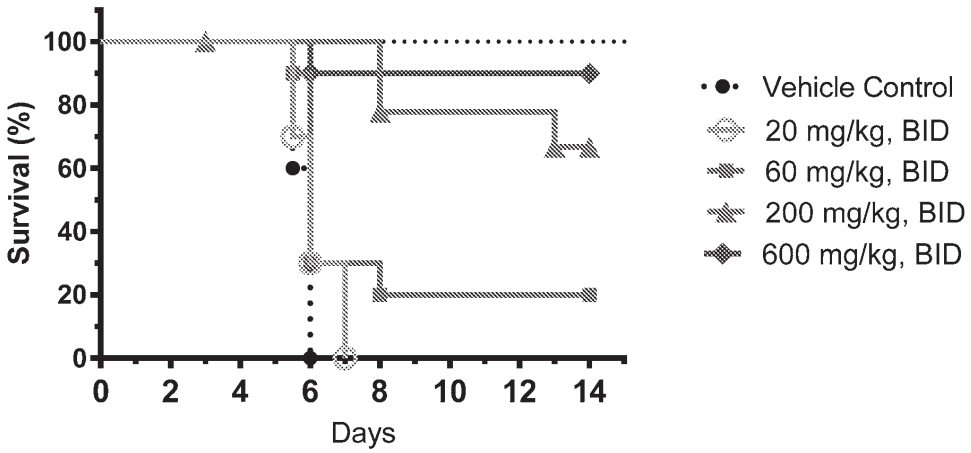

Survival (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14
Days
Vehicle Control
20 mg/kg, BID
60 mg/kg, BID
200 mg/kg, BID
600 mg/kg, BID

FIG. 18

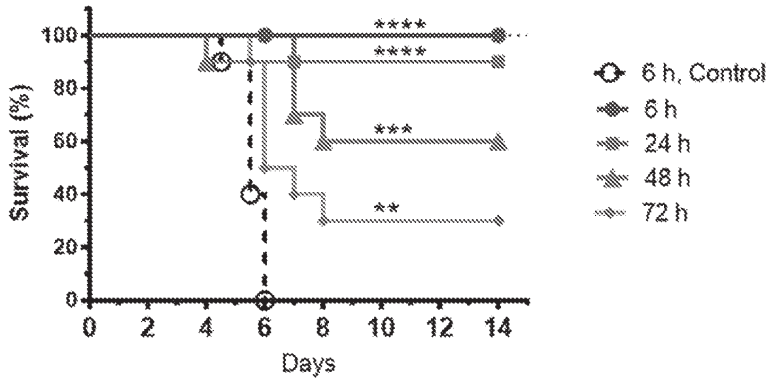

Survival (%)
100
80
60
40
20
0
0 2 4 6 8 10 12 14
Days
****
****
***
**
6 h, Control
6 h
24 h
48 h
72 h

FIG. 19

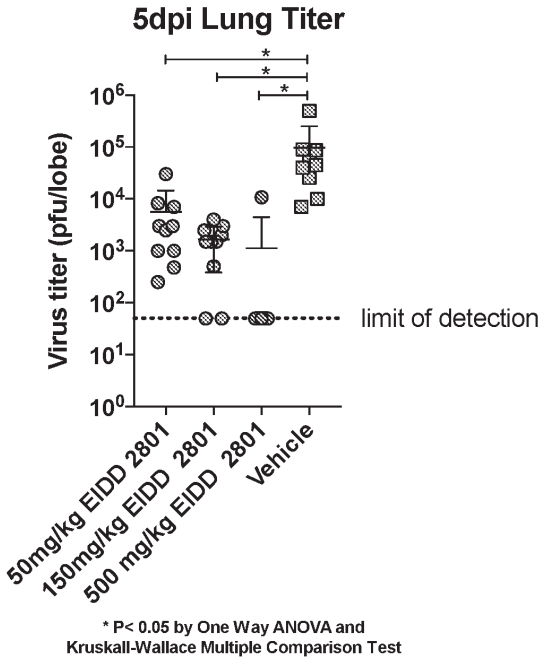

5dpi Lung Titer
Virus titer (pfu/lobe)
10^6
10^5
10^4
10^3
10^2
10^1
10^0
limit of detection
50mg/kg EIDD 2801
150mg/kg EIDD 2801
500 mg/kg EIDD 2801
Vehicle
* P< 0.05 by One Way ANOVA and
Kruskall-Wallace Multiple Comparison Test

FIG. 20

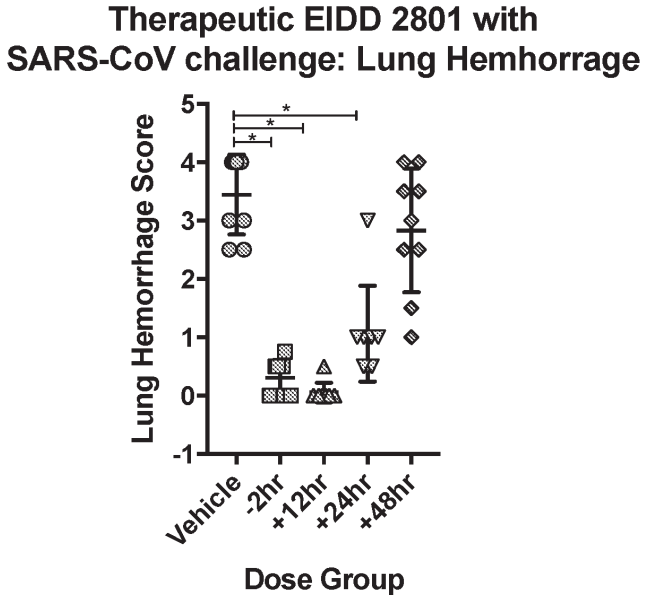

Therapeutic EIDD 2801 with
SARS-CoV challenge: Lung Hemhorrage
Lung Hemorrhage Score
5
4
3
2
1
0
-1
*
*
*
Vehicle
-2hr
+12hr
+24hr
+48hr
Dose Group

FIG. 21

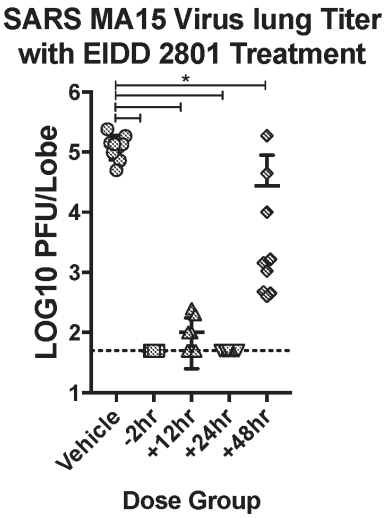

SARS MA15 Virus lung Titer
with EIDD 2801 Treatment
LOG10 PFU/Lobe
6
5
4
3
2
1
*
Vehicle
-2hr
+12hr
+24hr
+48hr
Dose Group

FIG. 22

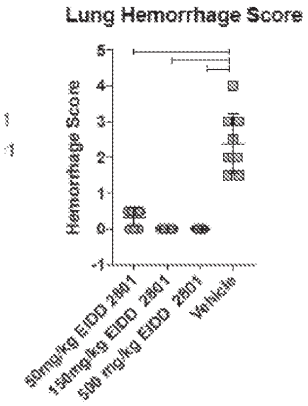

Lung Hemorrhage Score
Hemorrhage Score
5
4
3
2
1
0
-1
50mg/kg EIDD 2801
150mg/kg EIDD 2801
500 mg/kg EIDD 2801
Vehicle

FIG. 23