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OVERVIEW OF EIDD-2801 (MK-4482)

A Direct-Acting Oral, Broad-Spectrum Antiviral Agent in Clinical Development for COVID-19

Special isirv-AVG Virtual Conference on 'Therapeutics for COVID-19'

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EIDD-2801: An Orally Administered Direct Acting Antiviral Agent

- EIDD-2801 is an orally administered prodrug of the direct acting antiviral agent EIDD-1931. Once in the plasma EIDD-2801 is rapidly converted by esterases to EIDD-1931 and is further converted intracellularly into the EIDD-1931 5'-triphosphate.
- EIDD-1931 (N-hydroxycytidine (NHC)) is broadly active with demonstrated antiviral activity in cellular models of infection against highly pathogenic coronaviruses including SARS, MERS and SARS-CoV-2, and animal models of SARS/MERS
- EIDD-1931 is effective in animal models of influenza (seasonal, pandemic, and avian), respiratory syncytial virus, and Venezuelan equine encephalitis virus
- EIDD-1931 is rapidly transported out of plasma into tissues important in the pathogenesis of SARS-CoV-2 infection. Particularly high levels are achieved in the lungs. EIDD-1931 is transported into the CNS.
- There is an extremely high barrier to resistance
- Phase 1 study complete: EIDD-2801 generally safe and well tolerated at all doses tested (up to 800 mg BID for 5.5 days). MTD not reached.
- Phase 2 virology studies underway in outpatients and hospitalized patients
- Phase 2/3 studies to be initiated.

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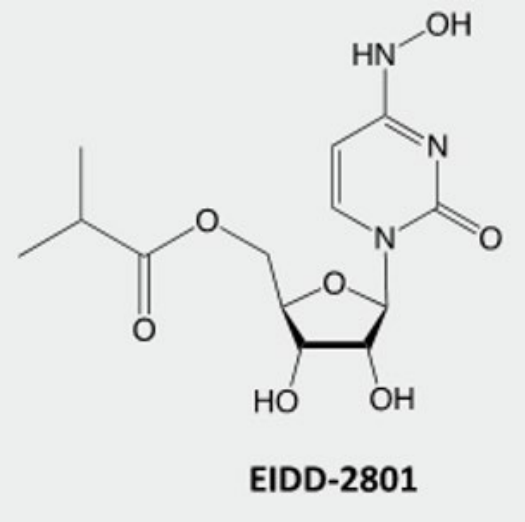
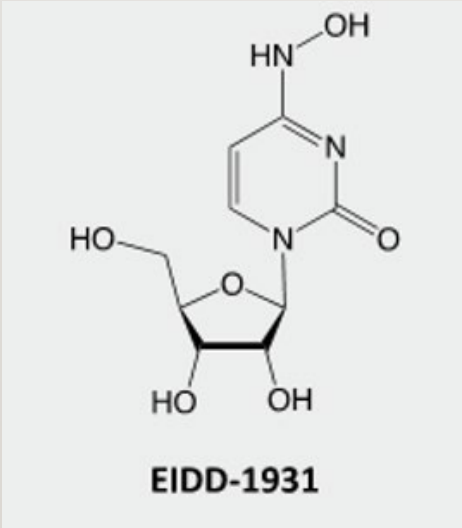
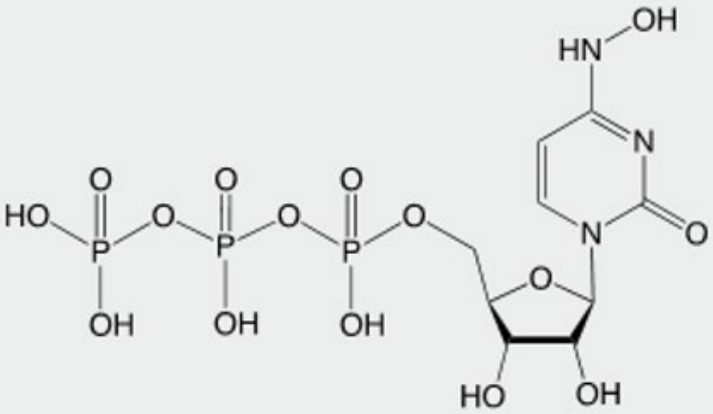
Structures Of EIDD-2801, EIDD-1931 and EIDD-1931 5’-triphosphate



EIDD-2801



EIDD-1931



EIDD-1931-5’-Triphosphate

Mechanism Of Action

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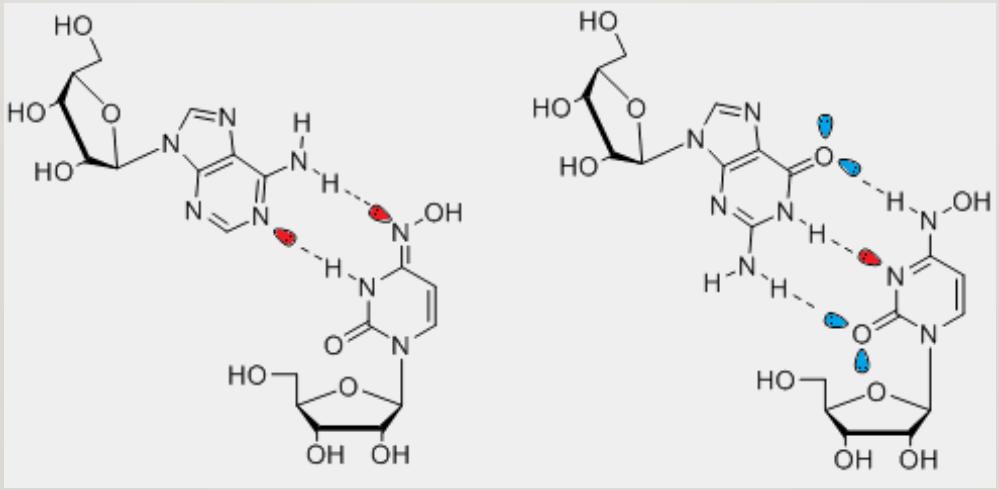
EIDD-1931 can Tautomerize and Mimic both Uridine and Cytidine



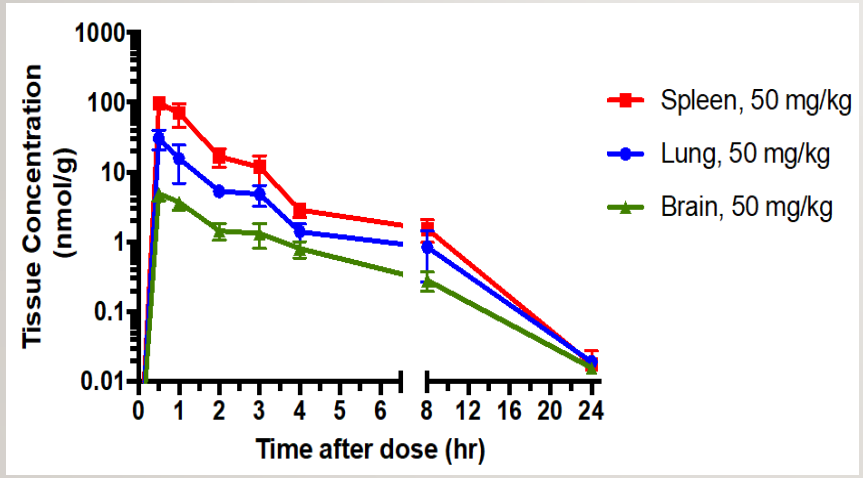
Uridine **Cytidine**

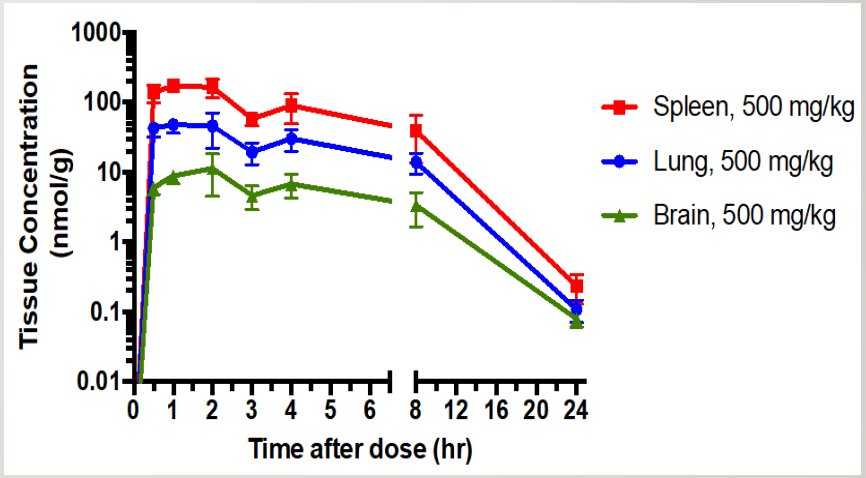
EIDD-1931 targets the virally encoded RNA-directed RNA polymerase, a highly conserved enzyme responsible for the synthesis of genomic and messenger RNAs. As a consequence of tautomerization, EIDD-1931 can pair with adenosine or guanosine. Over time this results in an accumulation of mutations that ultimately leads to viral ablation.

Adapted from: Moriyam, K. *Nucleic Acids Research* **1998**, **26** (9), 2015-2111

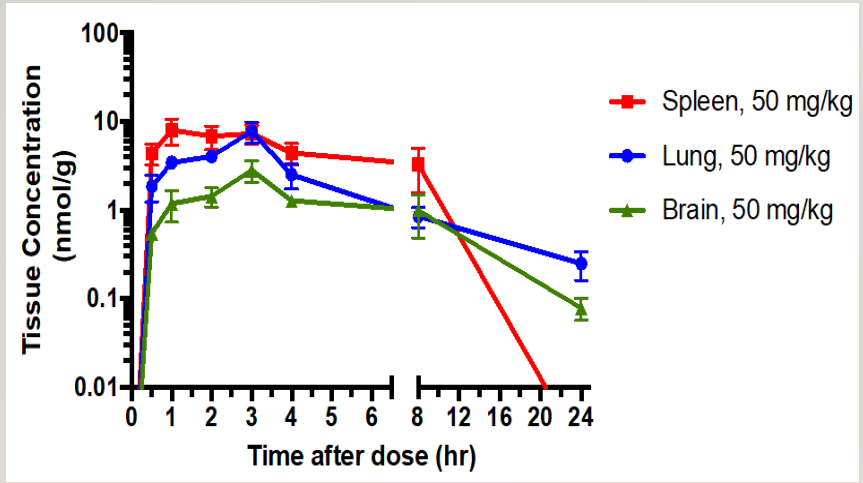
EIDD-1931 Is Efficiently Distributed To And Anabolized In Key Tissues In The Pathogenesis Of RNA Viral Disease

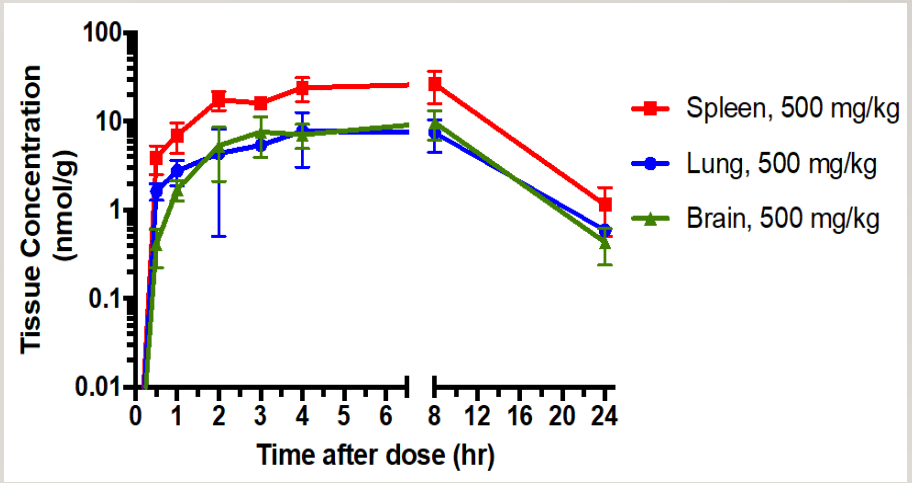
EIDD-1931 levels in mouse tissues after a single oral dose





EIDD-1931 5'-triphosphate in mouse tissues after a single dose of EIDD-1931





Painter et al., *Antiviral Res.*, Vol 171, Nov. 2019

ß-D-N4-Hydroxycytidine (EIDD-1931) Potently Inhibits SARS-CoV-2 Replication

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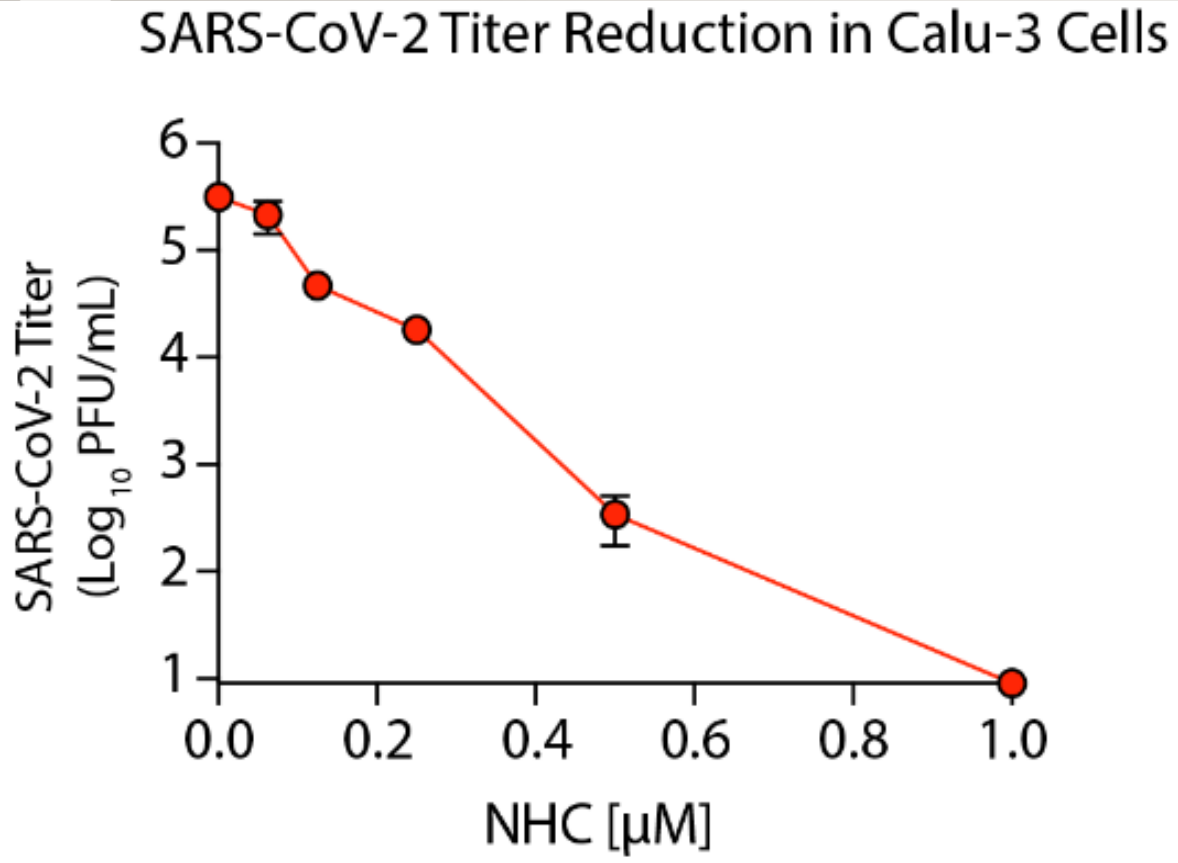

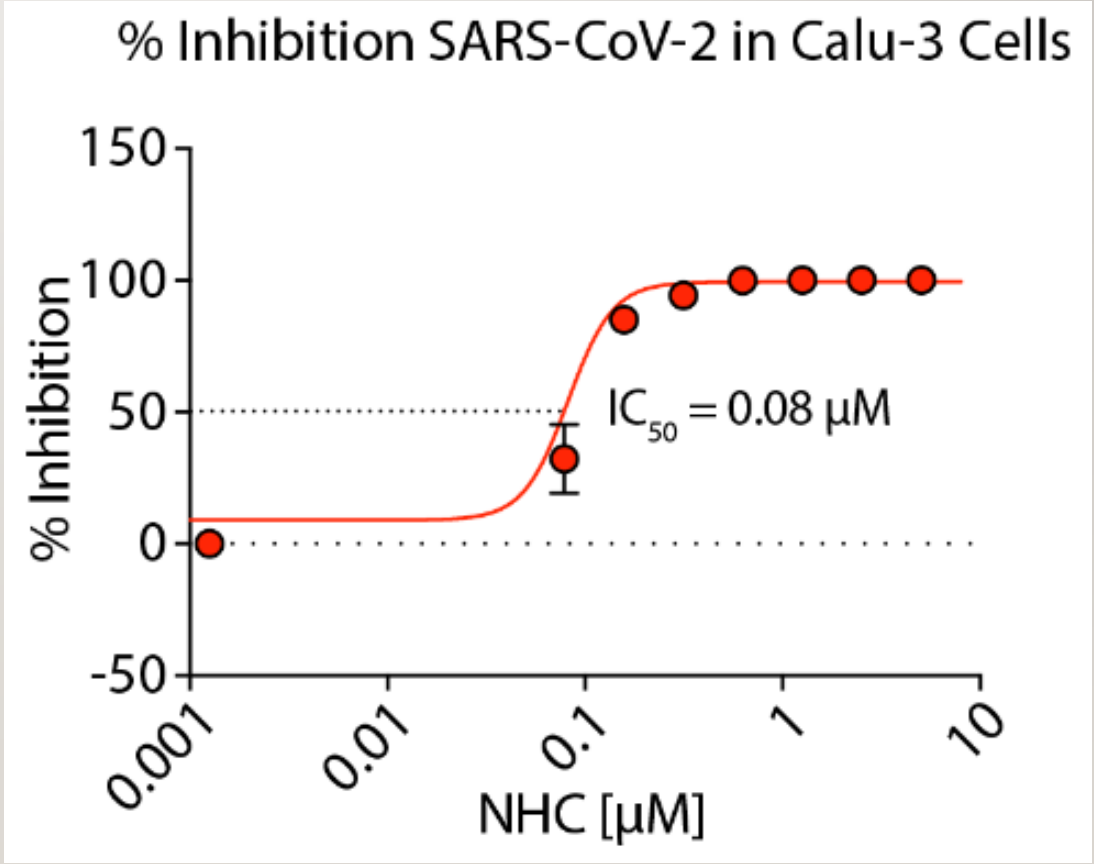

Cells were infected with a MOI of 0.1 for 30 min, washed and exposed to a dose response of NHC in triplicate per condition

Sheahan et al., Sci, Trans. Med., Vol 12 Issue 541, 29 April, 20

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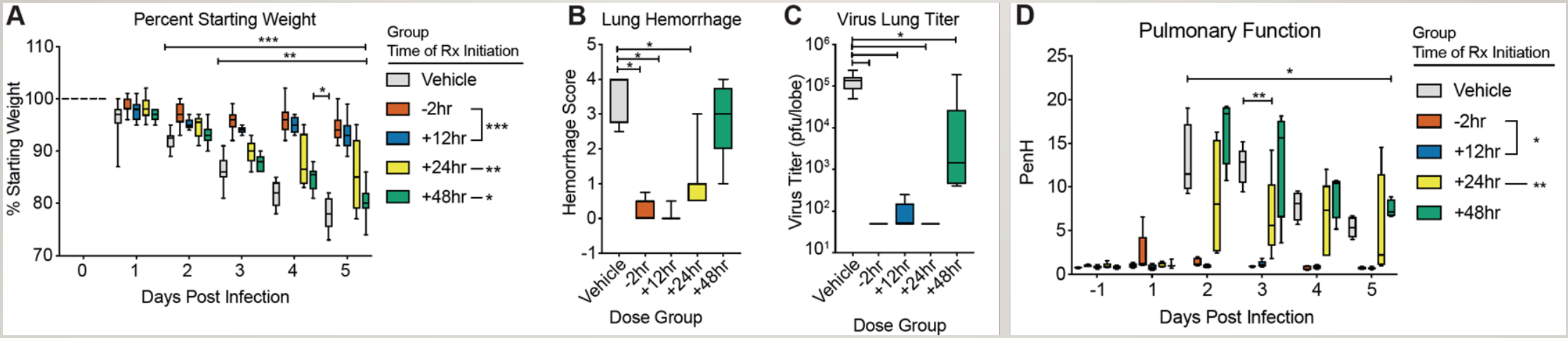
EIDD-1931 Is A Ribonucleoside Analog With Broad Activity Against Respiratory Viruses

Virus	EC_{50}(μM)	CC_{50}(μM)	Selectivity Index	Assay
CHKV	1.0	338	≥300	Plaque reduction assay in Vero cells
VEEV	1.4	>500	≥300	Plaque reduction assay in Vero cells
WEEV	0.73	247	≥300	Neutral Red CPE assay in Vero 76 cells
EEEV	0.93	123	132	Visual CPE assay in Vero 76 cells
Human-CoV	0.20	224	≥1100	Neutral Red CPE assay in HEL cells
SARS-CoV	<0.4	139	≥300	Neutral Red CPE assay in Vero 76 cells
MERS-CoV	<0.8	20	>25	TCID50 viral titer reduction assay in VeroE6 cells
Ebola	4.7	>100	>21	Plaque reduction assay in Vero cells
RSV	2.5	>300	>120	Replicon assay in Huh-7 cells
Enterovirus-68	2.3	52	23	Neutral Red CPE assay in RD cells
Enterovirus-71	2.3	48	21	Neutral Red CPE assay in Vero 76 cells
Rhinovirus	0.48	44	92	Neutral Red CPE assay in HeLa cells
Influenza A (H1N1)	1.1	>300	>270	HAU titer assay in MDCK cells
Influenza B (Yamagata)	0.015	>100	≥6000	HAU titer assay in MDCK cells

Therapeutic Treatment with EIDD-2801 is Effective in Reducing SARS-CoV Viral Load and Pathogenesis in a Mouse Model

C57BL/6 mice (n=5) were infected with mouse adapted SARS-CoV (SARS-MA15)
EIDD-2801 treatment (PO, b.i.d.) was performed starting (-2), 12, 24 and 48 hours post-infection (hpi)



- EIDD-2801 treatment initiated 12 and 24 hpi prevented body weight loss. Treatment initiated at 48 hpi partially protected from body weight loss;
- EIDD-2801 significantly reduced lung hemorrhage when treatment initiated at 12 or 24 hr after infection;
- All EIDD-2801 treated mice had significantly reduced viral loads in the lungs;
- EIDD-2801 treatment initiated 12 hr after infection completely abrogated the loss of pulmonary function (assessed via whole body plethysmography)

Sheahan et. al., *Science Translational Medicine* 12(541),2020.

Therapeutic Treatment with EIDD-2801 is Effective in Reducing MERS-CoV Replication and Pathogenesis in a Mouse Model

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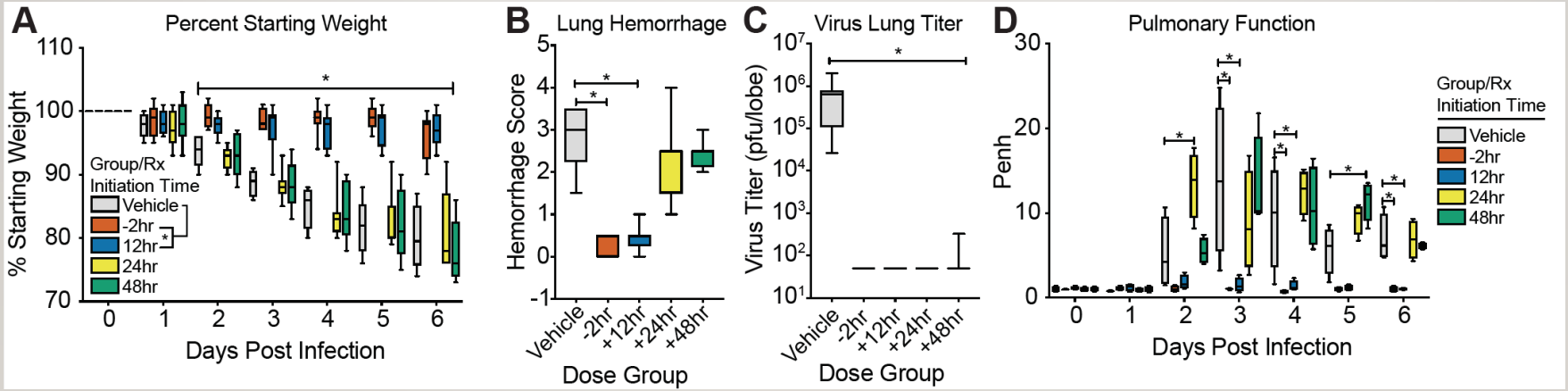
Mice genetically modified to be permissive for MERS infection (n=5) were infected with MERS-CoV p35C4 strain
EIDD-2801 treatment (PO, b.i.d.) was performed starting (-2), 12, 24, or 48 hours post-infection



- EIDD-2801 treatment initiated 12hr after MERS-CoV infection prevented body weight loss and lung hemorrhage measured on 6 dpi (not at 24 or 48 hpi)
- All EIDD-2801 treated mice had virus lung titer on 6 dpi reduced to the limit of detection in all treatment groups;
- EIDD-2801 treatment initiated 12 hr after infection completely prevented the loss of pulmonary function (assessed via whole body plethysmography)

EIDD-2801 Is Effective In The Ferret Model Of Influenza

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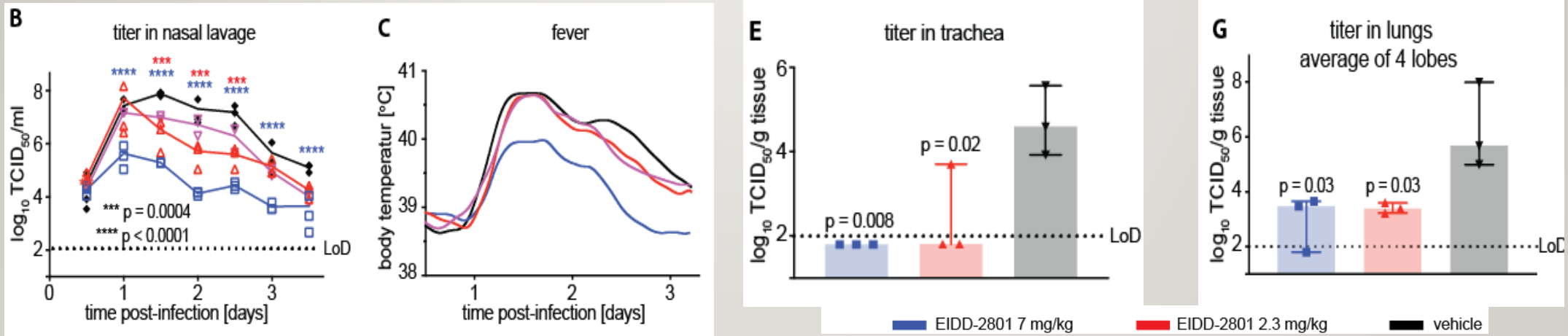
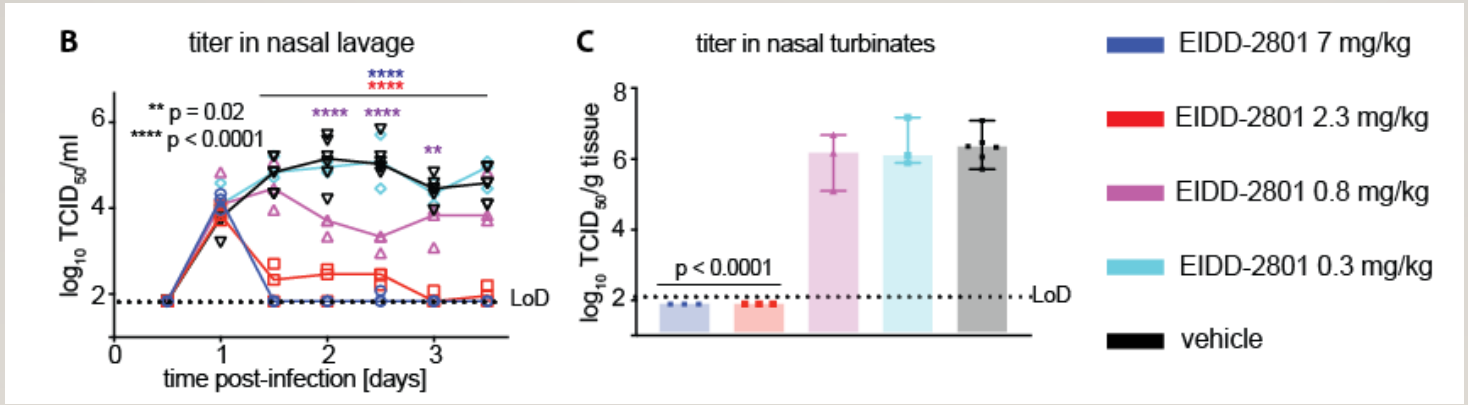
Pandemic A/Ca/07/2009 (H1N1) stain:



Seasonal A/Wi/67/2005 (H3N2) stain:



Minimal efficacious dose:

- pandemic H1N1 – 7 mg/kg
- seasonal H3N2 – 2.3 mg/kg

Toots et al. *Science Translational Medicine*, 2019 Oct 23;11(515)

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Unique Opportunity for Rapid Start-up of Clinical Studies Allowed for Accelerated Phase 1 Data Collection

- EIDD-2801 development underway since 2016 (EIDD-1931 program initiated in 2013)
- IND for Influenza filed in March, 2020
- First-in-Human dosing began in April, 2020
- Phase 2 COVID-19 Study was enabled in June, 2020 as safety data became available for potentially efficacious doses
- Extraordinary efforts by regulatory agencies, a clinical research organization, ethics committees, principal investigators, and nonclinical/clinical teams provided the platform for rapid start-up and rapid enrollment in the Phase 1 and early Phase 2 programs

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A Randomized, Double-Blind, Placebo-controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Administration to Healthy Volunteers

Study Start Date: 10 April 2020 Completion date: 08 Aug 2020 (4 months to complete) 130 Enrolled

- Part 1: single oral doses of EIDD-2801 or Placebo in cohorts of 8 subjects each randomized 3:1
- Part 2: two single oral doses of EIDD-2801 in a cohort of 10 administered in an open-label manner
- Part 3: twice daily oral doses of EIDD-2801 or Placebo in cohorts of 8 subjects each randomized 3:1
- Single doses of 50 to 1600 mg and multiple doses of 50 mg to 800 mg BID for 5.5 days
- Generally safe and well tolerated at all doses tested (maximum tolerated dose not reached)
- Pharmacokinetics of EIDD-1931 were dose proportional with generally low variability
- Dosing with food resulted in modest decrease in C_{max} and prolongation of half-life with little change in AUC
- Exposures achieved predicted to be in therapeutic range for SARS-CoV-2 and influenza

https://clinicaltrials.gov/ct2/show/record/NCT04392219

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A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19

Primary Virology Outcome Measure: Days until non-detectable SARS-CoV-2 in nasopharyngeal swabs in each randomized arm

Primary Safety Outcome Measure: Number of participants with any adverse events (AE) leading to discontinuation of treatment, study drug-related discontinuation of treatment, or new grade 3 or higher AEs

Infectious Virus Isolation will be performed

Key Inclusion Criteria: at least 18 years old at screening, within 7 days of symptom onset, experiencing symptoms of COVID-19, has a positive test for COVID-19

Key Exclusion Criteria: does not require hospitalization, does not have significant kidney or liver disease or major bleed, has not received other therapeutic interventions for COVID-19

Randomized (EIDD-2801:PBO) treatment for 5 days (po BID) with follow-up through 28 days

Frequent nasopharyngeal swabs for qPCR and viral culture; safety labs; symptom diary

Up to 5 dose cohorts planned

https://clinicaltrials.gov/ct2/show/NCT04405570

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The Safety of EIDD-2801 and its Effect on Viral Shedding of SARS-CoV-2 (END-COVID)

Primary Outcome Measures:

- Number of Participants that achieve Virologic Clearance after oral administration of EIDD-2801 (qPCR)
- Number of Participants with any Serious Adverse Events as assessed by DAIDS AE grading scale
- Number of Participants with any Adverse Events as assessed by DAIDS grading scale

SARS-CoV-2 infectivity assays will be performed

Key Inclusion Criteria: at least 18 years old and hospitalized at screening, within 7 days of symptom onset, experiencing symptoms of COVID-19, has a positive test for COVID-19

Key Exclusion Criteria: does not require mechanical ventilation, does not have active cancer, organ transplant, end-organ kidney disease, decompensated liver disease or congestive heart failure, major bleed, or baseline supplemental oxygen requirement

Randomized (EIDD-2801:PBO) treatment for 5 days (po BID) with follow-up through 28 days

Frequent nasopharyngeal swabs for qPCR and viral culture; safety labs; symptom diary

Approximately 5 dose cohorts planned

https://clinicaltrials.gov/ct2/show/NCT04405739

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AGILE-ACCORD: A Randomized, Multicentre, Seamless, Adaptive Phase I/II Platform Study to Determine the Optimal Dose, Safety, and Efficacy of Multiple Candidate Agents for the Treatment of COVID-19: A structured summary of a study protocol for a randomized platform trial

Objectives: Phase I: To determine the optimal dose of each candidate entered into the platform

Phase II: To determine the efficacy and safety of each candidate entered into the platform, compared to current Standard of Care (SoC), and recommend whether it should be evaluated further in later Phase II and III platforms

Trial design:

- Bayesian multicenter, multi-arm, multi-dose, multi-stage open-label, adaptive, seamless phase I/II randomized platform trial to determine the optimal dose, activity and safety of multiple candidate agents for the treatment of COVID-19
- Master Protocol with each candidate evaluated with its own Candidate Specific Trial (outpatients with mild/moderate disease)
- Randomised 2:1 candidate:SoC in cohorts of 6 (approximately 3 cohorts)
- Expansion into Phase II once dose has been identified based on safety
- Main outcomes: Dose-limiting toxicities (CTCAE) for Phase I, Candidate-specific for Phase II (Virology)

https://doi.org/10.1186/s13063-020-04473-1