

**The nucleoside analog antiviral CMX521
inhibits SARS-CoV-2 in human airway
epithelial cell cultures and exhibits
prophylactic and therapeutic efficacy
against respiratory disease in a mouse
model of SARS-CoV-2 infection**

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Forward-Looking Statements

These slides contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks and uncertainties that could cause actual results to differ materially from those projected. Among the factors and risks that could cause actual results to differ materially from those indicated in the forward-looking statements are risks that the current pre-clinical or clinical study data for CMX521 will not support accelerated, or any, regulatory approval; risks that ongoing or future studies/trials may not be successful or replicate previous trial results, or may not be predictive of real-world results or of results in subsequent trials; risks and uncertainties relating to competitive products and technological changes that may limit demand for our drugs; risks that our drugs may be precluded from commercialization by the proprietary rights of third parties; and additional risks set forth in the Company's filings with the Securities and Exchange Commission. These forward-looking statements represent the Company's judgment as of the date of this release. The Company disclaims, however, any intent or obligation to update these forward-looking statements.



Novel coronavirus outbreaks occurring every 6-8 years

8,000

SARS-CoV Outbreak (2002 – 2004)

- 9.6% case fatality rate (CFR)
- 774 fatalities attributed

2,500

MERS-CoV (2012 – 2021+)

- 35% CFR
- 889 fatalities attributed

>450mm

SARS-CoV-2 (2019 – 2022+)

- Highly infectious with a 1-2% CFR
- >6 million fatalities attributed

What's Next ?

CMX521: Direct-acting antiviral delivered to key site of viral replication to enhance efficacy and safety



CMX521...

- Ribonucleoside triphosphate inhibits norovirus RdRp*
- Oral formulation developed through Phase I
- Excellent safety profile in GLP tox studies
- No significant inhibition of human DNA polymerase α , β , or γ , RNA polymerase Type II or mitochondrial RNA polymerase at $\leq 200 \mu\text{M}$ CMX521-TP
- Well-tolerated in healthy volunteer Phase I study up to highest dose tested (2400 mg)

*Confirmation in SARS-CoV-2 RdRp ongoing



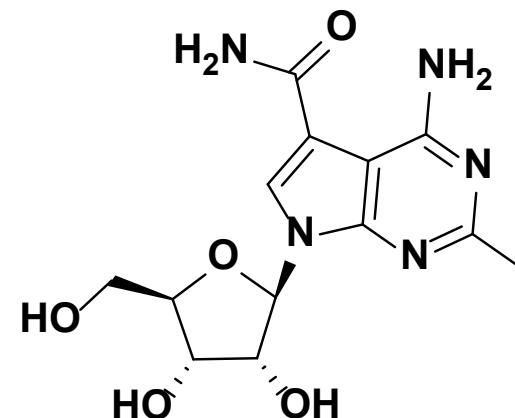
...for SARS-CoV-2

- Low μM in vitro activity across diverse coronaviruses
- In vivo efficacy in SARS-CoV-2-MA10 mouse-model
- Inhalation administration maximizes respiratory exposure while minimizing systemic exposure
- Primed for rapid development to clinical POC due to prior development through Phase I

Oral CMX521 formulation developed through Phase 1 study

Favorable safety profile in nonclinical species and humans with well-characterized nonclinical ADME profile

- CMX521 not mutagenic, clastogenic, cytotoxic or mitotoxic and demonstrated no significant off-target pharmacology
- Oral formulation developed for norovirus disease
- 7-day repeat dose LOAEL plasma exposures in dog > 10x human plasma exposure with 2.4 g oral dose
 - No adverse toxicity identified in rat with 14-days repeat dosing ≤ 2000 mg/kg/day
 - Mouse PK study exhibited low plasma exposure with inhaled administration of efficacious doses
- Phase 1 single ascending dose study in healthy volunteers (≤ 2400 mg; n = 38 subjects)
 - No SAE's, AE-related withdrawals, clinically significant changes in vital signs, ECGs or clinical laboratory parameters and no dose or exposure relationship to TEAEs
- Well-characterized metabolic and transporter interaction profile
 - Minimal DDI potential
 - Elimination primarily via urine and bile as parent
 - Characterization of nucleoside and efflux transporters complete
- Drug substance process robust and scalable to large kg scale batches
 - Manufactured 20 kg GMP clinical batch; stability > 36 months
 - Polymorph study completed enabling post-POC formulation optimization



The coronavirus RdRp active site is highly conserved

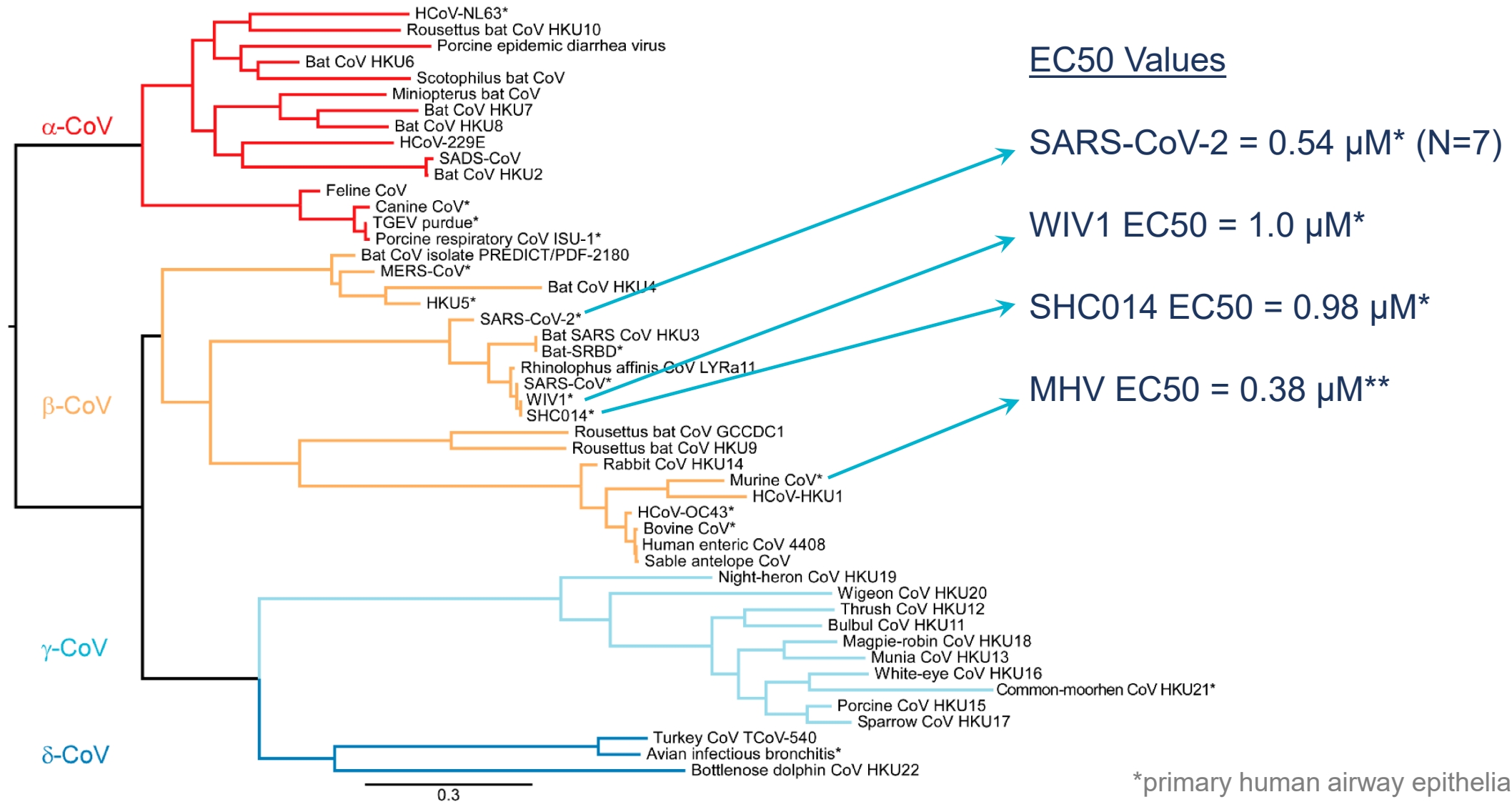
Amino acids involved in RNA/nucleotide binding, remdesivir binding, catalysis are nearly identical across relevant species

RdRp Codon	452	498	500	501	502	545	555	557	559	565	569	573	577	590	592	594	618	619	621	622	623
SARS-CoV-2	D	L	K	S	A	K	R	V	G	T	R	Q	K	G	S	F	D	Y	K	C	D
SARS	D	L	K	S	A	K	R	V	G	T	R	Q	K	G	S	F	D	Y	K	C	D
MERS	D	L	K	S	A	K	R	V	G	T	R	Q	K	G	T	F	D	Y	K	C	D
MHV	D	Y	K	S	A	K	R	V	G	T	R	Q	K	G	T	F	D	Y	K	C	D

RdRp Codon	682	683	684	685	687	688	691	758	759	760	761	813	814	832	840	857	858	862	864	865	
SARS-CoV-2	S	G	D	A	T	A	N	L	S	D	D	C	S	P	A	E	R	L	I	D	-
SARS	S	G	D	A	T	A	N	L	S	D	D	C	S	P	A	E	R	L	I	D	-
MERS	S	G	D	A	T	A	N	L	S	D	D	C	S	P	A	E	R	L	I	D	-
MHV	S	G	D	A	T	A	N	L	S	D	D	C	S	P	A	E	R	L	I	D	-

- Residues involved in RNA/nucleotide binding, remdesivir binding (yellow), and catalysis (green) are shown (GenBank).
- Amino acid positions numbered according to SARS-CoV-2 (GenBank YP_009725307); other sequences: SARS-CoV-1 (GenBank QJE50587); MERS (GenBank AFY13306); murine hepatitis virus, MHV (GenBank NP_045299)

CMX521 in vitro activity against β -coronaviruses



*primary human airway epithelial cells

**DBT cells (mouse brain tumor cells)

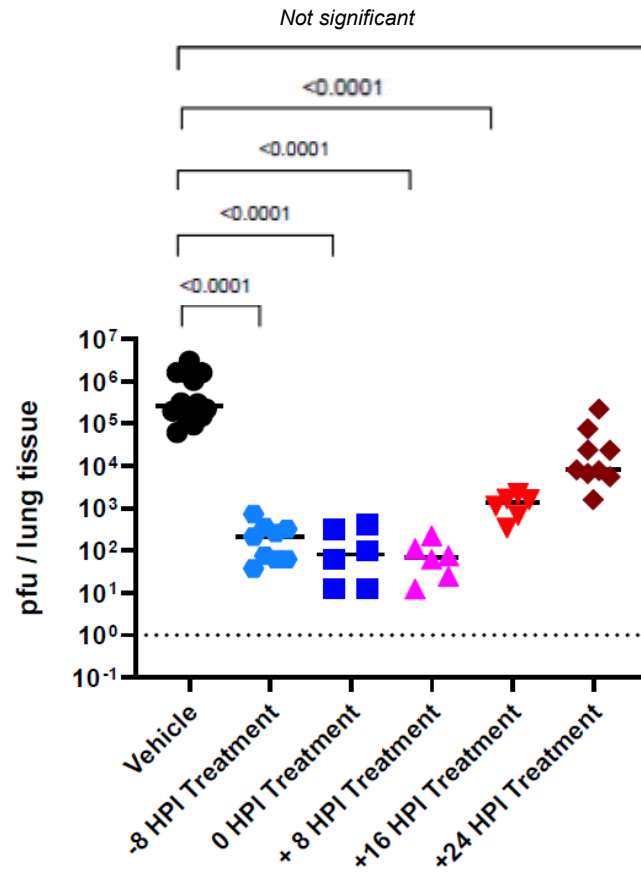
Collaboration with UNC employed a preclinical SARS-CoV-2 model

- Mouse-adapted SARS-CoV-2-MA10 model
 - Intranasal infection
 - Replicates lung pathology of human infection at 4-days post infection
 - Adjusted disease course suggests 1 day in mouse \approx 5-7 days in human
- CMX521 delivered as inhaled nebulized liquid aerosol
 - Simple, pH-adjusted saline formulation well-tolerated
 - 5 mg (dose delivered to chamber) every 8 hours from initiation to Day 4
 - CMX521-TP detected in 5/5 mouse lung lobes up to 8 hours after single administration of inhaled aerosolized CMX521
 - Minimal systemic exposure
- Clinical observations and virology outcomes

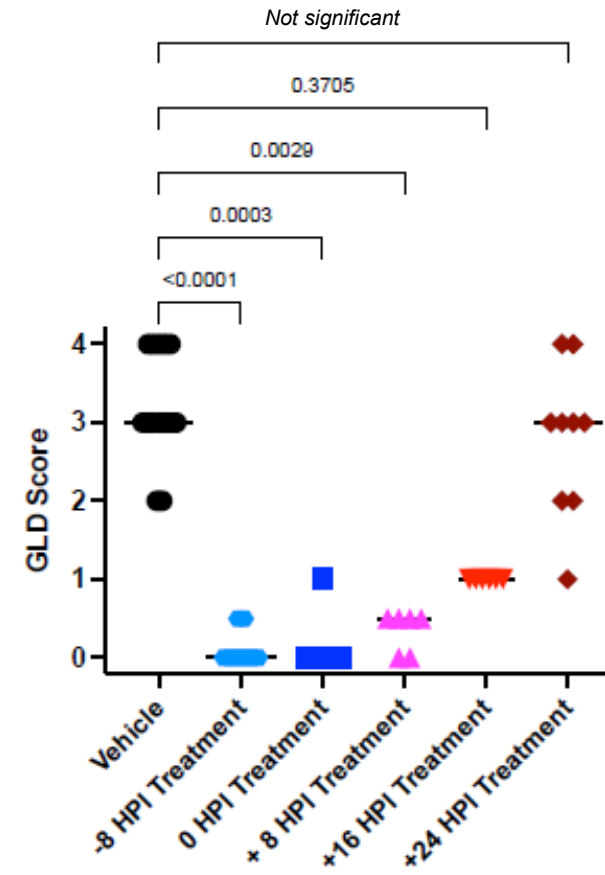


CMX521 treatment initiated ≤ 16 hr post-infection significantly improved titers and lung pathology at Day 4

Viral Lung Titer *Replicating SARS-COV-2-MA10*

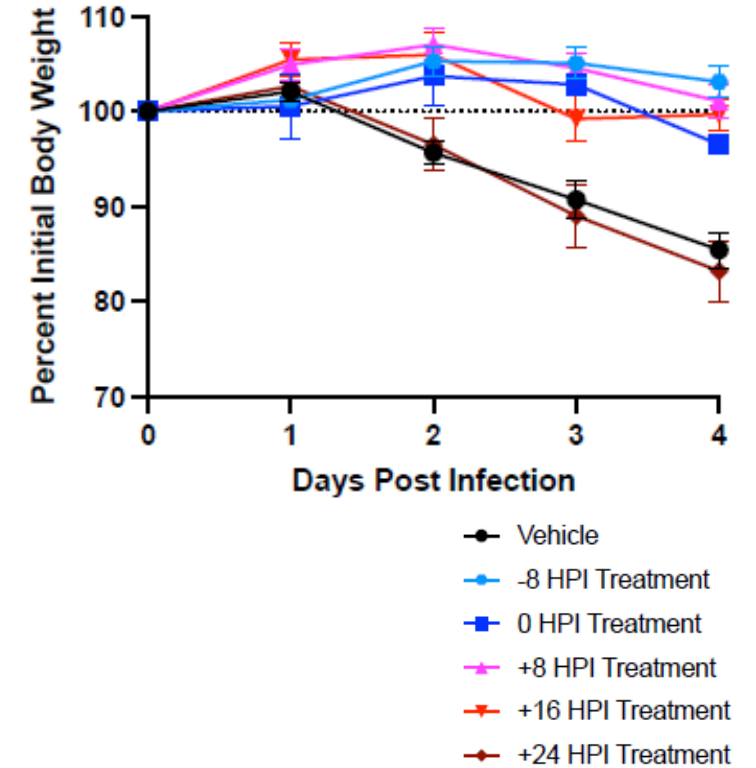
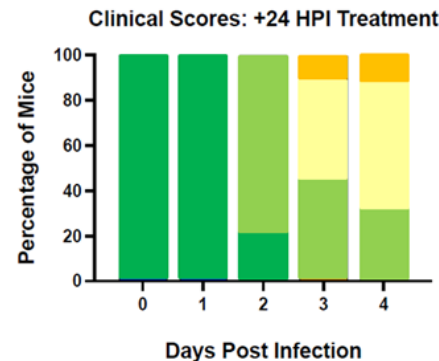
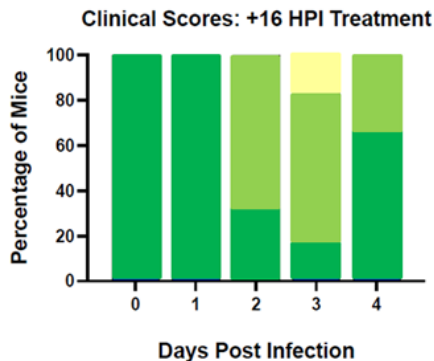
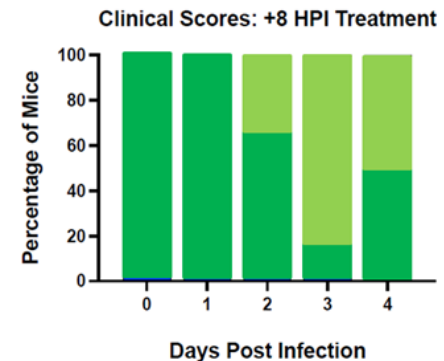
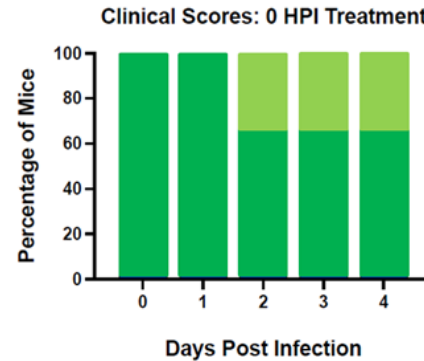
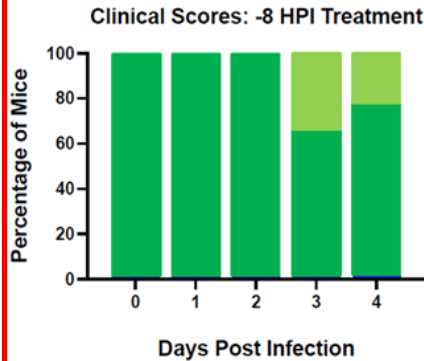
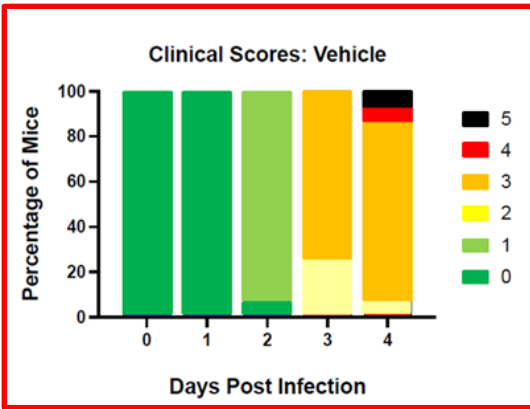


Lung Pathology *Gross lung discoloration (GLD)*



Adjusted disease course suggests 1 day in mouse equals ~5-7 days in humans

CMX521 treatment ≤ 16 hr post-infection protected mice from body weight loss and clinical symptoms of disease



0 = normal, 1 = unkempt coat, 2 = (1)+hunched posture, 3 = (2)+ reduced movement, 4 = minimal spontaneous movement +/- dyspnea (humane endpoint) 5 = moribund / dead / euthanized

- Prophylactic treatment initiation demonstrates strong effect on clinical scores versus vehicle
- Post-infection treatment initiation ≤ 16 hr demonstrates similar protection against adverse clinical endpoints

NOTE: Pie-cage aerosol delivery/handling accelerates progression of disease by ~24 hours

Potential for rapid bridging program to drive CMX521 to IND with inhaled formulation

Pharmacology

Dose-range in mouse model
Confirmation of MoA
Complete resistance passaging
Evaluate potential combinations

Formulation / Dose Selection

Formulation optimization
Nonclinical assessment of deposited dose
Clinical dose selection

Toxicology

7d GLP rat bridging study
7d GLP dog bridging study

CMC

Characterization & modelling of deposited dose in human
Analytical method development & characterization of formulation

Potential to initiate clinical POC within 1 year



Major Scientific Contributors to SARS-CoV-2 Effort on CMX521

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