Pharmacokinetics (PK) and Safety of a First-in-Class Antiviral (CMX521) for Human Norovirus in Healthy Adult Subjects

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BACKGROUND

- Norovirus (NV) is a common cause of acute gastroenteritis (~700 million global cases annually).
- There are no approved products for the prevention or treatment of human NV infections.
- CMX521 is a first-in-class antiviral in development for prevention and treatment of human NV.
- CMX521, a nucleoside analog, is selectively active against the highly conserved NV polymerase.
- CMX521 demonstrates pan-genotypic activity against diverse strains of NV *in vitro*, inhibition of murine NV replication in mice, and low systemic exposure in rats.
- The active antiviral, CMX521-triphosphate, is formed rapidly upon cell entry.
- An oral NV antiviral drug with relatively low systemic absorption could target intestinal enterocytes where NV replicates, while minimizing potential side effects associated with high systemic exposure.

OBJECTIVE

- To characterize the safety and plasma PK of single oral doses of CMX521 in healthy adult subjects.

METHODS

Study Design

- Randomized; Double-Blinded; Placebo-Controlled; Single Ascending Dose.
- Eligible subjects were male and female healthy adults (age 18-60 yr.) not taking any prescription or non-prescription medications or herbal products.
- Subjects were randomized to receive a single oral dose of CMX521 or placebo, in 5 sequential ascending dose cohorts (Table 1).
- The 200 mg starting dose was selected by applying a 10-fold reduction to the human equivalent dose of the single no-observed-adverse-effect level (NOAEL) dose in dog (2000 mg).

Table 1. Study Treatment Design

Cohort	CMX521 / Placebo (n / n)	Dose (mg)
1	4 / 2	200
2	6 / 2	400
3	6 / 2	800
4	6 / 2	1600
5	6 / 2	2400

PK Data

- Blood samples were collected from each subject at specified time points (immediately prior to the dose, and at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 10.5, 11, 11.5, 12, 13, 14, 24, 24.5, 25, 26, 27, 48, 72, and 96 hours post dose) for measurement of CMX521 concentrations in plasma.
- CMX521 plasma concentrations were measured using a validated HPLC MS method with an analytical range of detection from 1.00 to 1000 ng/ml.
- CMX521 plasma PK parameters were determined using Phoenix® 8.0 software and noncompartmental approaches, and summarized by dose using descriptive statistics.

Safety and Tolerability Data

- Safety was actively monitored for each subject from baseline through Day 14 post dose:
  - Vital signs, physical examination, and electrocardiogram.
  - Blood samples for hematology and chemistry, and urinalysis.
  - Adverse events.

RESULTS

Demographics

Table 2. Baseline Demographics

	200 mg	400 mg	800 mg	1600 mg	2400 mg	PBO	Total
Age, years (mean ± SD) Range, years [range]	48 ± 9.0 [35-59]	30 ± 8.6 [20-45]	36 ± 17.7 [19-55]	24 ± 2.5 [21-26]	25 ± 3.3 [21-30]	35 ± 13.2 [18-58]	33 ± 13.0 [18-59]
Male Female	2 2	6 0	4 2	6 0	6 0	9 1	33 5
Race							
White	3	3	5	5	5	9	30
Black/African	0	0	0	0	1	0	1
Asian	0	2	0	0	0	0	2
Other	1	1	1	1	0	1	5
BMI, kg/m² (mean ± SD) Range, kg/m² [range]	26.4 ± 2.2 [23.6-28.8]	24.9 ± 1.2 [23.3- 26.4]	25.9 ± 2.6 [22.4-30.0]	25.6 ± 2.2 [23.1-29.5]	25.1 ± 3.3 [21.6-29.0]	24.6 ± 4.0 [19.2-31.2]	25.3 ± 2.8 [19.2-31.2]

PBO = Pooled placebo SD = standard deviation BMI = body mass index

PK Summary

- CMX521 was rapidly absorbed from the gastrointestinal tract (median Tmax range: 1-1.5 hours) (Table 3).
- Increasing single doses of CMX521 resulted in less-than-dose-proportional increases in the geometric mean plasma Cmax and the AUC (Table 3 and Figure 1).
- Small transient increases in CMX521 mean plasma concentration were noted, beginning at 4, 10, and 24 hours post dose (Figure 1: inset), which corresponded to the times of the controlled-access meals provided to the subjects at the study site.

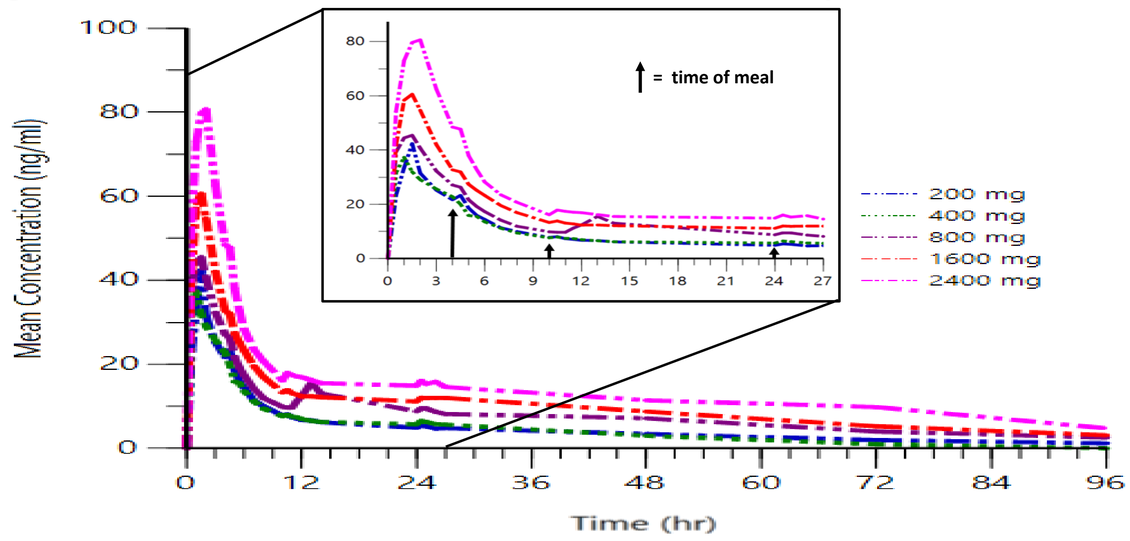
RESULTS (continued)

Table 3. CMX521 Plasma PK Characteristics by Treatment

Plasma PK Parameter	200 mg	400 mg	800 mg	1600 mg	2400 mg
C_{max} (ng/mL) *	38.9 (68.9%) [24.3 – 96.3]	39.3 (31.2%) [25.8 – 54.1]	48.3 (21.8%) [32.9 – 58.9]	69.2 (39.4%) [42.5 – 103]	91.9 (33.9%) [50.0 – 131]
T_{max} (hr) ^	1.25 [1 .00– 1.50]	1.00 [0.50 – 3.00]	1.50 [0.50 – 3.00]	1.25 [0.50 – 2.00]	1.50 [0.50 – 2.00]
AUC_{0-24} (hr.ng/mL) *	259 (35.9%) [179 - 390]	262 (28.5%) [191 – 430]	385 (20.7%) [283 – 492]	426 (51.8%) [241 – 897]	612 (28.3%) [390 – 861]
AUC_{last} (hr.ng/ml) *	438 (44.1%) [241 – 590]	399 (29.7%) [264 – 589]	747 (28.2%) [572 – 1240]	893 (49.4%) [524 – 1710]	1270 (42.7%) [720 – 2210]

*Data are presented as: geometric mean; (coefficient of variation % of geometric mean); [range]
^Data are presented as: median; [range]

Figure 1. Mean Plasma CMX521 Concentration vs. Nominal Time by Treatment



Safety Summary

- No clinically significant laboratory or electrocardiogram findings were noted.
- No serious treatment-emergent adverse events (TEAE) were reported.
- 4 subjects who received CMX521 experienced a study drug-related TEAE (Table 4).
  - 3 events were mild, 1 event was moderate, and all resolved in ≤ 2 days.
  - No subjects who received 1600 mg or 2400 mg of CMX521 experienced a study drug-related TEAE.
- 12 other subjects experienced a TEAE assessed as not related to study drug.
- There was no CMX521 dose or exposure relationship to the TEAEs.

Table 4: Study Drug-Related TEAEs by SOC and PT

System Organ Class (SOC) Preferred Term (PT)	200 mg (N = 4)	400 mg (N = 6)	800 mg (N = 6)	1600 mg (N = 6)	2400 mg (N = 6)	PBO (N = 10)
Gastrointestinal disorders Diarrhoea	0	0	1 (16.7%)	0	0	0
General disorders and administration site conditions Influenza like illness	1 (25.0%)	0	0	0	0	0
Metabolism and nutrition disorders Decreased appetite	0	1 (16.7%)	0	0	0	0
Musculoskeletal and connective tissue disorders Pain in extremity	1 (25.0%)	0	0	0	0	0
Nervous system disorders Headache	0	0	0	0	0	1 (10.0%)

PBO = Pooled placebo N = number of subjects studied; ( ) = percentage of subjects with a study drug-related TEAE

CONCLUSIONS

- **CMX521 plasma exposures increased in a less-than-proportional manner with escalating single oral dose administration.**
- **Single oral doses of CMX521 up to 2400 mg were generally well-tolerated. No safety concerns were identified.**
- **These data support continuing the development of CMX521 for human norovirus infections.**

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DISCLOSURES

- This study was sponsored by Chimerix, Inc., Durham, NC, USA. All authors are employees or contractors of Chimerix, Inc.

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