

## BACKGROUND

Tenofovir (TFV) is a nucleotide analogue whose active form, TFV diphosphate (TDP), inhibits reverse transcription of hepatitis B virus (HBV). TDP is the active metabolite of HBV treatments TFV disoproxil fumarate (TDF, Viread®, Gilead Sciences) and TFV alafenamide (TAF, Vemlidy®, Gilead Sciences), both oral prodrugs of TFV.

NCO-48 Fumarate is a novel Liver-Targeted Prodrug (LTP) of TFV. The liver-targeting capability of oral NCO-48 Fumarate is based on a chemical modification of TFV into an inactive prodrug form that is rapidly absorbed and efficiently activated to TDP in the liver. This leads to high TDP concentrations in the liver, the site for HBV replication, and low levels of TFV in the systemic circulation and kidney, a target organ for TFV toxicities. By targeting the release of TDP to the liver, it is expected that NCO-48 Fumarate can minimize kidney and bone toxicity by reducing systemic exposure of TFV compared with TDF and TAF.

This first-in-human study evaluated the safety and tolerability of a range of single oral doses of NCO-48 Fumarate in healthy subjects and characterized the PK profile of NCO-48 Fumarate and its active metabolite, TFV, in healthy subjects under fed and fasted conditions.

## OBJECTIVES

### Primary Objective:

- To evaluate the safety and tolerability of single oral doses of NCO-48 Fumarate in healthy subjects

### Secondary Objective:

- To evaluate the pharmacokinetic (PK) profile of NCO-48 Fumarate and its active metabolite, tenofovir (TFV), following single oral doses
- To evaluate the effect of food on the PK of a 30 mg dose of NCO-48 Fumarate

## METHODS

- Phase 1, ascending, single-dose, double blind, placebo-controlled study in healthy male and female subjects (NCT04309526)
- A total of 48 subjects were enrolled in the study as 6 groups (N = 8/group; 6 active and 2 placebo)
- Subjects received single doses of NCO-48 Fumarate (2, 10, 30, 60, 120, or 240 mg) or placebo. Food effect was evaluated in the 30 mg dose group
- All subjects were admitted on Day 1 and observed throughout the morning of Day 3. Safety assessments and NCO-48 Fumarate and TFV PK sample collection (blood and urine) occurred during this time
- Subjects were discharged after 48-hour assessments and returned to the study site on Days 5 and 7 (final visit) for follow-up procedures
- In the 30 mg dose group, the fed and fasted doses were separated by a minimum of 14 days

## RESULTS

### SUBJECT DEMOGRAPHICS

- 47 subjects completed the study; 1 subject in 30 mg fed group withdrew

Normal Healthy Subjects	NCO-48 Fumarate						Pooled Placebo (N=12)
	2 mg (N=6)	10 mg (N=6)	30 mg (N=6)	60 mg (N=6)	120 mg (N=6)	240 mg (N=6)	
Age, yrs (SD)	44.7 (13.2)	35.7 (13.8)	44.3 (17.6)	46.2 (9.9)	37.7 (17.3)	35.3 (14.2)	45.8 (13.9)
Gender, n (%)	Female 3 (50.0)	4 (66.7)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	5 (41.7)
	Male 3 (50.0)	2 (33.3)	5 (83.3)	2 (33.3)	4 (66.7)	5 (83.3)	7 (58.3)
Race, n (%)	White 4 (66.7)	2 (33.3)	2 (33.3)	1 (16.7)	5 (83.3)	3 (50.0)	5 (41.7)
	Black 2 (33.3)	4 (66.7)	4 (66.7)	4 (66.7)	1 (16.7)	3 (50.0)	6 (50.0)
	Other 0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Weight, kg (SD)	81.0 (9.8)	75.0 (7.6)	85.5 (10.5)	81.6 (11.3)	88.2 (13.9)	77.2 (5.1)	74.1 (8.1)
BMI, kg/m <sup>2</sup> (SD)	27.1 (2.1)	27.2 (2.45)	27.4 (2.2)	26.6 (2.5)	27.2 (3.4)	25.2 (3.6)	25.3 (3.1)

### SAFETY

- NCO-48 Fumarate was safe and well tolerated at single oral doses from 2 mg to 240 mg
- No subject had a serious adverse event (AE) or were discontinued due to a treatment-emergent AE (TEAE)
- There were no clinically significant or dose-dependent changes in hematology, clinical chemistry, urinalysis, electrocardiograms, or vital signs
- Eleven TEAEs were reported by 8 NCO-48 Fumarate subjects and 1 by a placebo subject; only 1 of the adverse events was considered drug-related (dyspepsia in 30 mg NCO-48 Fumarate, fasting)

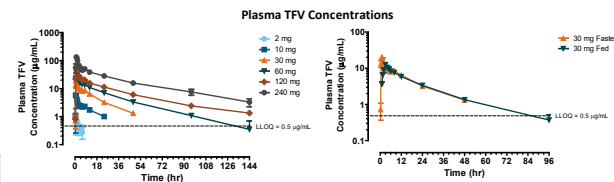
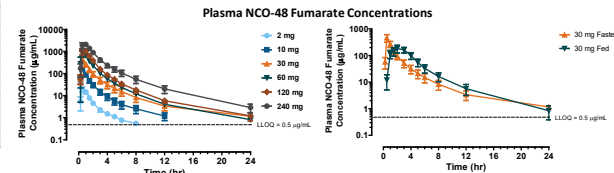
Category	NCO-48 Fumarate						Pooled Placebo (N=12)
	2 mg (N=6)	10 mg (N=6)	30 mg (N=6)	60 mg (N=6)	120 mg (N=6)	240 mg (N=6)	
Subjects with any TEAE (%)	1 (16.7)	3 (50)	1 (16.7)	1 (20.0)	1 (16.7)	0 (0.0)	1 (8.3)
Study drug related TEAE (%)		1 (16.7)					
Headache/lightheadedness	1 (16.7)	1 (16.7)			1 (16.7)		
Urinary tract infection		1 (16.7)					
Vomiting		1 (16.7)					
Abdominal pain				1 (20.0)			
Diarrhea				1 (20.0)			
Lower back pain		1 (16.7)					
Dyspepsia			1 (16.7)				
Skin rash							1 (8.3)
Pruritus							1 (8.3)

### PHARMACOKINETICS

- NCO-48 Fumarate was readily absorbed and converted to TFV at all doses
- Mean plasma concentrations of NCO-48 Fumarate and TFV increased dose proportionately, and C<sub>max</sub> and area under the concentration versus time curve (AUC) increased in a dose-dependent manner
- C<sub>max</sub> of NCO-48 Fumarate and TFV were observed (T<sub>max</sub>) within 2 hours (h) and ~1 h after dosing, respectively, across all groups
- The mean elimination half-life (t<sub>1/2</sub>) of NCO-48 Fumarate and TFV ranged from 1 - 4 h and 20 - 45 h, respectively

### PHARMACOKINETICS, CON'T

- Absorption of NCO-48 Fumarate was delayed after high-fat food consumption, but overall exposure was comparable with fasted administration
- Amount of NCO-48 Fumarate and TFV excreted in the urine increased with NCO-48 Fumarate dose level. However, in the 24 h period post dose <0.5% was excreted unchanged and <10% TFV, indicating the primary source of elimination was not renal



Dose Group	NCO-48 Fumarate						TFV					
	AUC <sub>0-24</sub> (h <sup>2</sup> ·µg/mL)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	Excreted in Urine (%)	AUC <sub>0-24</sub> (h <sup>2</sup> ·µg/mL)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	Excreted in Urine (%)		
2 mg	27.75 (14.07)	21.87 (11.17)	0.5 (0.5, 1.0)	1.34 (0.39)	0.11 (0.06)	3.28 (1.58)	0.99 (0.27)	1.0 (0.5, 1.0)	NA (3.89)	7.71 (3.89)		
10 mg	208.66 (98.01)	189.33 (91.26)	0.5 (0.25, 1.0)	1.98 (0.58)	0.18 (0.10)	46.58 (7.22)	6.32 (0.815)	1.0 (0.5, 1.5)	20.005 (23.89)	6.64 (1.03)		
30 mg	622.51 (423.21)	473.50 (352.70)	0.5 (0.5, 1.0)	2.76 (1.17)	0.18 (0.09)	166.97 (48.18)	20.60 (7.24)	1.0 (0.5, 1.0)	28.67 (23.89)	7.975 (2.45)		
30 mg (Fed)	716.59 (480.99)	397.78 (120.65)	2.0 (1.5, 3.0)	3.07 (1.18)	0.24 (0.16)	145.375 (25.82)	12.84 (2.67)	3.0 (3.0, 5.0)	22.76 (8.00)	7.05 (1.11)		
60 mg	1307.67 (451.33)	954.50 (509.47)	0.75 (0.5, 1.0)	3.42 (0.95)	0.20 (0.08)	306.16 (49.63)	39.52 (8.69)	1.0 (0.5, 1.0)	40.26 (13.35)	7.345 (1.35)		
120 mg	1919.53 (601.22)	1364.17 (456.67)	0.75 (0.5, 1.0)	4.01 (0.81)	0.25 (0.14)	449.55 (56.67)	60.43 (9.25)	1.0 (0.5, 1.5)	44.36 (7.49)	6.48 (0.49)		
240 mg	4348.03 (2121.00)	2490.00 (982.73)	0.75 (0.5, 1.0)	4.04 (0.86)	0.24 (0.11)	1101.66 (240.11)	138.17 (21.61)	1.0 (0.5, 1.5)	44.85 (7.90)	5.285 (3.4)		

\*Mean (SD); †median (min, max); NA, not available

## CONCLUSIONS

NCO-48 Fumarate is a promising agent for the treatment of HBV, demonstrating excellent PK properties and safety after a single dose. NCO-48 Fumarate is currently in a multiple-dose clinical trial in HBV patients (NCT04629976).