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LIST OF ABBREVIATIONS, ACRONYMS AND DEFINITION OF TERMS

This list serves as the first use of an abbreviation, acronym, or term.

Abbreviation/Acronym	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\ 24hr}$	Area under the concentration-time curve from time 0 to 24 hours
$AUC_{0\ 72hr}$	Area under the concentration-time curve from time 0 to 72 hours
AUC_{Day1}	Area under the concentration-time curve from time 0 to Day 1
AUC_{Day7}	Area under the concentration-time curve from time 0 to Day 7
$AUC_{0\ inf}$	Area under the concentration-time curve from time 0 to infinity
AUC_{inf}	Area under the concentration-time curve extrapolated to infinity
AUC_{last}	Area under the concentration-time curve from time 0 through the last measurable concentration
CEDU	5-(2-chloroethyl)-2 -deoxyuridine
CHO	Chinese hamster ovary
C_{max}	Maximum concentration
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
cps	Centipoise
CRL	Charles River Laboratories
DNA	Deoxyribonucleic acid
DRF	Dose range finding
ECG	Electrocardiograms
EFD	Embryo-fetal developmental
EIDD	Emory Institute for Drug Development
ENU	N-ethyl-N-nitrosourea

Abbreviation/Acronym	Definition
FDA	Food and Drug Administration
GD	Gestation day
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HCT	Hematocrit
HGB	Hemoglobin
hr	Hour(s)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
LD	Lactation day
LLOQ	Lower limit of quantitation
MN-PCE	Micronucleated polychromatic erythrocytes
MOV	Molnupiravir (MK-4482, EIDD-2801)
MTD	Maximum tolerated dose
NA	Not applicable
NHC	N-hydroxycytidine (EIDD-1931)
NHC-TP	N-hydroxycytidine-5′-triphosphate (EIDD-2061)
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OECD	Organisation for Economic Co-operation and Development
PBMC	Peripheral blood mononuclear cell
pEFD	Preliminary embryo-fetal developmental
PK	Pharmacokinetic(s)
PND	Postnatal day
QD	Once daily
Q3D	Once every 3 days
Q12H	Every 12 hours
RBC	Red blood cell(s)
RdRp	RNA-dependent RNA polymerase

Abbreviation/Acronym	Definition
RET	Reticulocyte(s)
ROS	Reactive oxygen species
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SARS-CoV-1	SARS-associated coronavirus-1
SARS-CoV-2	SARS-associated coronavirus-2
SD	Sprague-Dawley
SE	Standard error
$t_{1/2}$	Apparent terminal half-life
TK	Toxicokinetic(s)
T_{max}	Time of maximum concentration
TP	Triphosphate
USA	United States of America
VEEV	Venezuelan equine encephalitis virus
WBC	White blood cell(s)
WOCBP	Women of child bearing potential
WT	Wild-type

1 BRIEF SUMMARY

Molnupiravir (MOV; MK-4482) is the 5′-isobutyrate prodrug of the broadly active, antiviral ribonucleoside analog N-hydroxycytidine (NHC) developed for the oral treatment of adult patients with COVID-19. MOV is hydrolyzed by esterases either during or after absorption to deliver NHC into systemic circulation. Once distributed inside cells, NHC is phosphorylated to its corresponding triphosphate anabolite (NHC-TP) and acts as a competitive alternative substrate for virally encoded RdRp. MOV and NHC inhibit replication of viral pathogens from multiple RNA virus families, including pathogenic coronavirus such as SARS-CoV-2. Antiviral activity has been verified in animal models of coronavirus virus infection.

MOV, an oral direct-acting antiviral agent, will address the critical need for different therapeutic agents to treat COVID-19. MOV is administered orally enabling patients to initiate therapy in an outpatient setting. This flexibility in outpatient management would help to limit direct patient interactions with health care staff and decrease transmission risk, which is significant due to the highly contagious nature of SARS-CoV-2. In vitro, NHC has a high genetic barrier to the development of resistance in nonclinical models and retains activity against SARS-CoV-2 and MHV (a related coronavirus) harbouring remdesivir resistance-associated mutations in the viral polymerase.

The recommended dose of MOV in adults is 800 mg Q12H for 5 days. Nonclinical exposure multiples of NHC to humans were based on population pharmacokinetics analysis in adult patients with COVID-19 from Part 1 of P001 and P002 clinical trials, where a 800 mg Q12H MOV dose resulted in systemic mean exposures ($AUC_{0\ 24hr}$) of 75.6 µm*hr and C_{max} of 10.8 µM. MOV $AUC_{0\ 24hr}$ exposure multiples were not calculated given that MOV is rapidly hydrolyzed to NHC and is generally undetectable in human plasma (LOQ of 0.0152 µM). Of note, MOV and NHC C_{max} achieved in the nonclinical studies were much higher than the clinical C_{max} of 0.026 µM and 10.8 µM, respectively, in COVID-19 patients at the clinical dose of 800 mg Q12H.

MOV was evaluated in genotoxicity assays (including Ames assays, in vitro and in vivo micronucleus assays, an in vivo Pig-a assay in rats, and an in vivo mutation assay in Big Blue® transgenic rats), tolerability/DRF studies in mice, rats, and dogs, repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs, fertility studies in male and female rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a pre- and post-natal developmental toxicity study in rats. Additional non pivotal short-term tolerability and/or TK studies were conducted in mice, rats, rabbits, and monkeys.

A summary of the studies conducted as part of the MOV toxicology program is presented in [Table 2.6.6: 1] and [Sec. 2.6.7: 1]. All pivotal toxicity studies were conducted in accordance with the principles of GLP. All studies were conducted at [redacted] USA [redacted] USA [redacted] USA [redacted] USA [redacted] USA [redacted] USA [redacted] USA [redacted] USA [redacted] USA; Merck Research

Laboratories, West Point, Pennsylvania USA; or [redacted] Canada. The USA and Canada are members of OECD and therefore part of the OECD Mutual Acceptance of Data system. GLP Compliance statements are included in all pertaining study reports. All pivotal studies were supported by toxicokinetic evaluation of MOV and NHC within the study or from studies conducted under the same conditions, utilizing identical doses administered using the same formulation [Sec. 2.6.7: 2]; [Sec. 2.6.7: 3]. Test article batches used in the GLP nonclinical studies are provided in [Sec. 2.6.7: 4].

Both the rat and dog are accepted animal models for the toxicological assessment of drugs as per current regulatory guidance (i.e., ICH M3[R2]: Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals). MOV has been shown to have acceptable in vitro and in vivo metabolism profiles and acceptable in vivo PK profiles in both rat and dog with formation of the NHC metabolite and NHC-TP anabolite in each species. The pharmacological target of NHC-TP is the exogenous viral RdRp.

The integrated assessment of the mutagenic and genotoxic potential of MOV indicates that MOV is not mutagenic or genotoxic in in vivo mammalian systems. MOV and NHC were positive in the in vitro bacterial reverse mutation assay (Ames assay) with and without metabolic activation. However, in two distinct in vivo rodent mutagenicity models dosed up to the maximum tolerated dose and at treatment durations and exposures exceeding those used in the clinic [Pig-a mutagenicity assay in rats and Big Blue® (*cII* Locus) transgenic rodent assay)], the impact of MOV treatment on mutation rates was not differentiable from mutation rates observed in untreated historical control animals. These whole animal models are robust tools for quantifying a drug's ability to induce mutations in vivo, and for assessment of human risk for mutagenicity. MOV was also negative for induction of chromosomal damage in in vitro micronucleus (with and without metabolic activation) and in vivo rat micronucleus assays. Based on the totality of the genotoxicity data, MOV is of low risk of genotoxicity in clinical use.

Target organs of toxicity identified in the repeat-dose toxicity studies were limited to bone marrow in dogs only, and growth plate in rats only. Bone marrow toxicity/hematopoietic findings (with resultant pancytopenia) were observed in the 28-day oral toxicity study in dogs at ≥17 mg/kg/day (0.4-fold the clinical NHC exposure at 800 mg Q12H). The adverse hematopoietic findings were dose related, affected all hematopoietic cell lines, caused subsequent mild hematological abnormalities on Day 7 and progressively more severe hematological changes after 14 to 21 days of continuous dosing, and were shown to be reversible. There were no hematologic changes indicative of bone marrow toxicity in clinical trials. In addition, there were no hematopoietic or hematological findings in the 28-day repeat-dose toxicity study in mice (19-fold the clinical NHC exposure at 800 mg Q12H), and in the 3-month repeat-dose toxicity study in rats (9.3/15-fold (female/male) the clinical NHC exposure at 800 mg Q12H).

Growth plate findings were observed in the bones in the 3-month oral toxicity study in rats, in males at ≥500 mg/kg/day (5.4-fold the clinical NHC exposure at 800 mg Q12H) and in

females at 1000 mg/kg/day (9.3-fold the clinical NHC exposure at 800 mg Q12H). The findings consisted of an increase in the thickness of the physis, associated with decreased bone formation at the end of long bones (femur, tibia) in males at 1000 mg/kg/day and thickening of the growth cartilage of the epiphysis of long bones and in patella of males and females at 1000 mg/kg/day. Minimal thickening of epiphyseal growth cartilage was also observed in males at 500 mg/kg/day. There were no changes observed in remaining tissues in the femorotibial joint, including articular surfaces, ligaments, synovial tissue, other soft tissue, and the cortical bone. There were no growth plate findings in rats dosed for 1 month up to 500 mg/kg/day (4.2/7.8-fold (female/male) the clinical NHC exposure at 800 mg Q12H), in dogs dosed for up to 14 days at 50 mg/kg/day (1.6-fold the clinical NHC exposure at 800 mg Q12H), or in mice dosed for 1 month at doses up to 2000 mg/kg/day (19-fold the clinical NHC exposure at 800 mg Q12H).

These growth plate findings are not relevant to adult humans because growth plates are no longer present in the mature skeleton of adult humans. The growth plate findings (observed in rats after 3 months of treatment, but not after 1-month of dosing) are of unclear significance in the context of short duration treatment in children. The findings were noted in rapidly growing rats (5 to 6 weeks of age at study start) that approximately doubled their body weights over the study duration. This very rapid bone growth cannot be directly translated to humans due to species-specific differences in skeletal development and bone turnover [Ref. 4.3: 05NK2R]. Additional cartilage findings observed only in the 3-month toxicity study in rats included a minimal to mild cytoplasmic alteration in chondrocytes of the tracheal cartilage in males only at ≥500 mg/kg/day. This was not associated with degenerative or inflammatory changes, did not impact the overall structure or integrity of the cartilage, did not impact airway size or diameter, and was consequently non-adverse. There were no growth plate or cartilage findings at 150 mg/kg/day in males (0.7-fold the clinical NHC exposure at 800 mg Q12H) and at 500 mg/kg/day in females (3.3-fold the clinical NHC exposure at 800 mg Q12H).

Additional findings including GI findings (e.g., stomach distention, emesis, diarrhea) and liver enzyme elevations were noted in the 7-day tolerability studies at high doses that exceeded the MTDs (2000 mg/kg/day in rats, 61/91-fold (female/male) the clinical NHC exposure at 800 mg Q12H and ≥300 mg/kg/day in dogs (19-fold the clinical NHC exposure at 800 mg Q12H). Liver enzyme elevations consisted of ≤2-fold increases in ALT and/or AST in rats at 2000 mg/kg/day, as well as approximately 2-fold increases in AST at 300 mg/kg/day in dogs, and up to 5-fold increases in ALP and ALT and 30-fold increases in AST at 1000 mg/kg/day in dogs (66-fold the clinical NHC exposure at 800 mg Q12H).

In fertility studies in rats there were no MOV-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.1/6.1-fold (female/male) the clinical NHC exposure at 800 mg Q12H). In pregnant rats administered MOV during the organogenesis period, developmental toxicity including embryolethality (post-implantation losses) and malformations/teratogenicity was observed at 1000 mg/kg/day (7.5-fold the clinical NHC exposure at 800 mg Q12H), and reduced fetal growth was noted at ≥500 mg/kg/day (≥2.9-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at doses up to 250 mg/kg/day (0.8-fold the clinical NHC exposure at

800 mg Q12H). Maternal toxicity included decreased food consumption and body weight losses, resulting in the early sacrifice of individuals at 1000 mg/kg/day, and decreased body weight gain at ≥500 mg/kg/day. In pregnant rabbits, developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (18-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity in rabbits at up to 400 mg/kg/day (6.5-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight gain, and abnormal fecal output at ≥400 mg/kg/day. In the pre- and postnatal developmental study in rats, there was no F0 maternal or F1 generation toxicity in up to the highest dose evaluated of 500 mg/kg/day (1.6-fold the clinical NHC exposure at 800 mg Q12H). While embryolethality (post-implantation losses) and teratogenicity were limited to rats exposed to 7.5-fold the clinical NHC exposure at 800 mg Q12H during the organogenesis period, and these developmental findings were not observed in rats up to 2.9-fold the clinical NHC exposure at 800 mg Q12H and rabbits up to 18-fold the clinical NHC exposure at 800 mg Q12H, the use of MOV is conservatively not recommended during pregnancy. WOCBP should use effective contraception for the duration of treatment and for at least 4 days after the last dose.

Collectively, these nonclinical data support the safe use of MOV for the treatment of COVID-19 in adult patients.

Table 2.6.6: 1 MOV Toxicology Program

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
Single-dose toxicity (Single dose MTD evaluation was included in Phase A of TT # [redacted] 7850, TT # [redacted] 7825, TT # [redacted] 7826 listed under Repeat dose toxicity below).					
Repeat-dose toxicity					
NHC: 1 Day MTD (Phase A) NHC: 7 Day (Phase B) Toxicity	Oral (gavage)	Mouse/Crl:CD1 ® (ICR)	500, 1000, 1500, 2000 0, 200, 500, 1000	NA	TT # [redacted] 7850 [redacted] [redacted] USA (Non GLP)
1 Day MTD (Phase A) 7 Day (Phase B) Toxicity & TK	Oral (gavage)	Rat/Hsd:SD	500, 1000, 1500, 2000 0, 200, 700, 2000	NA	TT # [redacted] 7825 [redacted] USA (Non GLP)
1 Day MTD (Phase A) 7 Day (Phase B) Toxicity & TK	Oral (gavage)	Dog (beagle)	300, 500, 1000, 2000 0, 100, 300, 1000	NA	TT # [redacted] 7826 [redacted] USA (Non GLP)

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
Repeat-dose toxicity					
28 Day Toxicity & TK	Oral (gavage)	Wild type Mouse/CByB6F1 Tg(HRAS)2Jic	0, 100, 300, 700, 2000	300	TT # [redacted] 9037 [redacted] USA (GLP)[a]
28 Day Toxicity & TK with 14 Day Recovery Period	Oral (gavage)	Rat/Hsd:SD	0, 50, 150, 500	≥500	TT # [redacted] 7814 [redacted] USA (GLP)
3 Month Toxicity & TK	Oral (gavage)	Rat/Crl:CD(SD)	0, 150 (males), 200 (females), 500, 1000	500 (females); 150 (males)	TT # [redacted] 1014 Merck Research Laboratories[b] West Point, PA, USA (GLP)
28 Day Toxicity & TK with 28 Day Recovery Period[b]	Oral (gavage)	Dog (beagle)	0, 6, 17, 50	6	TT # [redacted] 7815 [redacted] USA (GLP)[c]
Genotoxicity					
NHC: Microbial Mutagenesis Assay	In vitro	*Salmonella typhimurium* (TA1537, TA98, TA100, TA1535) and *Escherichia coli* (WP2 *uvrA*)	1.5 to 5000 µg/plate ± S9	Positive (WP2 *uvrA* +/ S9) Negative (TA98, TA100, TA1535, TA1537 +/ S9)	TT # [redacted] 7851 [redacted] USA (Non GLP)
Microbial Mutagenesis Assay	In vitro	*Salmonella typhimurium* (TA1537, TA98, TA100, TA102, TA1535) and *Escherichia coli* (WP2 *uvrA*)	25 to 5000 µg/plate (WP2 *uvrA* and TA102 ± S9); 1 to 1000 µg/plate (TA1537, TA98, TA100, TA1535 +S9); 50 to 5000 µg/plate (TA1537, TA98, TA100, TA1535 S9)	Positive (TA102, WP *uvrA* +/-S9) Negative (TA1537, TA98, TA100, TA1535 +/ S9)	TT # [redacted] 7810 [redacted] USA (GLP)[d]

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
Micronucleus Induction Assay	In vitro	TK6 cells	4 hr (S9) 82.5, 165, 330 µg/mL; 4 hr (+S9) 2.58, 20.6, 124 µg/mL; 27 hr (S9) 2.58, 61.9, 248 µg/mL	Negative	TT # 7806 [redacted] USA (GLP)[e]
Micronucleus Induction Assay	Oral (gavage)	Rat/Crl:CD(SD)	0, 500, 1000, 2000	Negative	TT # 7816 [redacted] USA (GLP)[f]
Mammalian Peripheral Blood Erythrocyte Pig a Mutation Assay	Oral (gavage)	Rat/Crl:CD(SD)	0, 50, 150, 500	Equivocal[f]	TT # 7808 [redacted] Canada (GLP)[g]
In Vivo Mutation Assay at *cII* Locus	Oral (gavage)	Rat (Big Blue® Transgenic F344)	0, 50, 150, 500	Negative	TT # 9025 [redacted] USA (GLP)
Reproductive and developmental toxicity					
Fertility (Female)	Oral (gavage)	Rat/Crl:CD(SD)	0, 100, 250, 500	≥500 (general toxicity and fertility)	TT # 9000 [redacted] USA (GLP)[h]
Fertility (Male)	Oral (gavage)	Rat/Crl:CD(SD)	0, 100, 250, 500	≥500 (general toxicity and fertility)	TT # 9012 [redacted] USA (GLP)[h]
Preliminary Embryo fetal Developmental & TK	Oral (gavage)	Rat/Crl:CD(SD)	0, 100, 200, 500, 1000	NA	TT # 7054 Merck Research Laboratories[b] West Point, Pennsylvania, USA (GLP)[i]

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
Embryo fetal Developmental & TK	Oral (gavage)	Rat/Crl:CD(SD)	0, 100, 250, 500	250 (maternal and developmental toxicity)	TT #[redacted] 7000 Merck Research Laboratories[b] West Point, Pennsylvania, USA (GLP)[h]
Preliminary Embryo fetal Developmental & TK	Oral (gavage)	Rabbit (Dutch Belted)	0, 60, 200, 500, 1000	NA	TT #[redacted] 7064 Merck Research Laboratories[b] West Point, Pennsylvania, USA (GLP)[j]
Embryo fetal Developmental & TK	Oral (gavage)	Rabbit (Dutch Belted)	0, 125, 400, 750	125 (maternal toxicity) and 400 (developmental toxicity)	TT #[redacted] 7010 Merck Research Laboratories[b] West Point, Pennsylvania, USA (GLP)[k]
Pre and Postnatal Development & TK	Oral (gavage)	Rat/Crl:CD(SD)	0, 100, 250, 500	≥500 (maternal and F_1 generation toxicity)	TT #[redacted] 9010 [redacted] USA (GLP)[l]
Local tolerance					
Bovine corneal opacity and permeability test	In vitro	Bovine corneas	0.75 g	NA	TT #[redacted] 7801 [redacted] USA (GLP)[m]
MatTek Epiderm™ MTT Viability Assay	In vitro	MatTek Epiderm™ tissue samples	100 mg	NA	TT #[redacted] 7802 [redacted] USA (GLP)[m]
Other toxicity studies					
Immunotoxicity					
Local Lymph Node Assay	Topical	Mouse (CBA/J)	25% (w/v MOV in DMF)	NA	TT #[redacted] 7803 [redacted] USA (GLP)[m]

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
Photoreactivity					
Photoreactivity Assay Reactive Oxygen Species (ROS)	In vitro	NA	200 µM	Non photoreactive	TT # [redacted] 7814 Merck Research Laboratories[b] West Point, Pennsylvania, USA (Non GLP)
Toxicokinetics					
7 Day TK	Oral (gavage)	Wild Type Mouse/CByB6F1 Tg(HRAS)2Jic	100, 300, 700, 2000	NA	TT # [redacted] 9011 [redacted] USA (GLP)
Exploratory 5 Day TK	Oral (gavage)	Rat/ Crl:CD(SD); Rat/Fischer 344: F344/NHsd	50, 150, 500,	NA	TT # [redacted] 1015 Merck Research Laboratories[b] West Point, Pennsylvania, USA (Non GLP)
Exploratory 14 Day Tolerability and TK	Oral (gavage)	Rabbit (Dutch Belted) Nonpregnant	0, 3, 30, 300, 1000	NA	TT # [redacted] 7043 Merck Research Laboratories[b] West Point, Pennsylvania, USA (Non GLP)
Exploratory 16 Day TK	Oral (gavage)	Dog/beagle	6 (QD), 17 (Q3D)	NA	TT # [redacted] 1005 Merck Research Laboratories[b] West Point, Pennsylvania, USA (Non GLP)
Other					
7 Day Dose Range Finding Assay	Oral (gavage)	Rat/Fischer 344: F344/NHsd	0, 250, 500	NA	TT # [redacted] 9027 [redacted] USA (Non GLP)

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
In Life Only: In vivo Mutation Assay at *cII* Locus	Oral (gavage)	Rat (Big Blue® Transgenic F344)	0, 50, 150, 500 Positive Control (20)	NA	TT # 9047 [redacted] USA (GLP)[n]
7 Day Tolerability	Oral (gavage)	Monkey (rhesus)	150, 300, 500	NA	TT # 7817 [redacted] USA (Non GLP)

[redacted]; DMF N,N Dimethylformamide; GLP Good Laboratory Practice; No. Number; [redacted]; MTD Maximum tolerated dose; MOV EIDD 2801; NA Not applicable; NHC N hydroxycytidine (EIDD 1931); NOAEL No observed adverse effect level; QD Once daily; Q3D Once every 3 days; SD Sprague Dawley; SN Study Number; TK Toxicokinetics.

[a] 28 day Wild Type CByB6F1 Tg(HRAS)2Jic mouse toxicity study (TT # 9037): GLP with the exception of bioanalysis and TK evaluation of NHC.

[b] Merck Research Laboratories is a division of Merck, Sharp, & Dohme Corp. (MSD).

[c] 28 day dog toxicity study (TT # 7815): Animals in the 50 mg/kg/day group received their last dose on Day 12 or 14, while animals in the 17 mg/kg/day group received their last dose on Day 21 (male) or 22 (female).

[d] In vitro microbial mutagenesis assay (TT # 7810): GLP [redacted].

[e] In vitro micronucleus assay in TK 6 cells (TT # 7806): GLP, [redacted].

[f] In vivo micronucleus assay (TT # 7816), in vivo Pig a assay (TT # 7808): GLP, [redacted].

[g] In vivo Pig a assay (TT # 7808): Results were considered equivocal since not all criteria for negative or positive response to mutagenicity were fulfilled.

[h] Fertility studies (TT # 9000 and TT # 9012): GLP, [redacted]

[i] Preliminary (TT # 7054) and definitive (TT # 7100) embryo fetal developmental studies in rats: GLP, [redacted]

[j] Preliminary embryo fetal developmental study in rabbits (TT # 7064): GLP, with the exception of bioanalytical sample results for NHC, [redacted]

[k] Definitive embryo fetal developmental studies in rabbits (TT # 7010): GLP, [redacted]

Footnotes continued on next page

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg/day)	Study Nos. Test Facility (GLP Status)
[l] Pre and Postnatal Developmental Toxicity study (TT # 9010): GLP, [redacted].					
[m] Occupational safety studies (TT # 7801, TT # 7802, TT # 7803): GLP [redacted].					
[n] In Life Only: In vivo Mutation Assay at *cII* Locus (TT # 9047): GLP [redacted]					

2 SINGLE-DOSE TOXICITY

Single-dose toxicity was evaluated as part of DRF studies (Phase A) in mice, rats, and dogs [Sec. 2.6.6: 3].

In a single-dose MTD Phase A study of NHC in mice, an oral dose of 500, 1000, 1500, or 2000 mg/kg was administered to Crl:CD1 mice (3/sex/group) (TT #-7850). No mortality occurred during Phase A. There were decreases in food consumption in both sexes at 1500 mg/kg and body weight loss in females at ≥1500 mg/kg, and decreased body weight gain in males at 2000 mg/kg during the first few days post-treatment.

In a single-dose MTD Phase A study of MOV in rats, an oral dose of 500, 1000, 1500, or 2000 mg/kg was administered to SD rats (2/sex/group) (TT #-7825). No mortality occurred during Phase A; the only MOV-related change was a mean weight loss of several grams for males and females at 2000 mg/kg during the first few days post-treatment, which correlated to 30% respective decreases in food consumption.

In a single-dose MTD Phase A study of MOV in dogs, an oral dose of 300, 500, 1000, or 2000 mg/kg was administered to beagle dogs (1/sex/group) (TT #-7826). No mortality occurred, and clinical signs were limited to minimal, transient GI effects, including emesis and soft feces at ≥300 mg/kg. All Phase A animals lost weight by Day 3, which corresponded to decreases in food consumption.

3 REPEAT-DOSE TOXICITY

3.1 Mice

3.1.1 NHC: Oral MTD/7-Day Dose-Range Finding in Mice (TT -7850)

The objective of this 2-phase non-GLP study was (1) to identify the single-dose MTD of NHC when administered to mice once via oral gavage (Phase A); and (2) to characterize the toxicity and TK of NHC when administered to mice by oral gavage once daily for up to 7 consecutive days (Phase B) [Sec. 2.6.7: 6].

Based on the results of single-dose Phase A (3 mice/sex/group) of the study, in which dose-limiting effects on mean food consumption and body weight were seen at doses of 1500 and

2000 mg/kg/day, dose levels of 200, 500, and 1000 mg/kg were chosen for Phase B (10 mice/sex/group), where animals received 7 consecutive daily doses. Mice were evaluated for standard in-life parameters followed by complete necropsy with organ weights. No histopathology was conducted. Plasma drug concentrations of NHC in treated samples were determined. Frozen tissues were collected for NHC and NHC-TP concentration analyses (liver, lung, spleen, brain, kidney, and heart) at 4 and 8 hours postdose. Accumulation of NHC and NHC-TP in these tissues was generally dose proportional.

No mortality occurred during either phase. During Phase A, the 500 and 1000 mg/kg doses were well tolerated. There were decreases in food consumption in both sexes and body weight loss in females at ≥1500 mg/kg, and decreased body weight gain in males at 2000 mg/kg.

During Phase B, 7 days of repeat dosing of the test article, NHC was well tolerated at dose levels of 200, 500, and 1000 mg/kg/day. No test article-related effects were noted in clinical observations, mean body weight, mean food consumption, clinical pathology parameters (hematology, clinical chemistry, and urinalysis), or anatomic pathology parameters (macroscopic observations and organ weights).

NHC TK parameters are presented in [Table 2.6.6: 2].

Table 2.6.6: 2 Plasma NHC TK Parameters in Mice Following Oral Dosing of NHC (TT #[redacted]-7850)

Dose Level (mg/kg)	Cmax (µM)	$AUC_{0\text{-}inf}$ (µM*hr)
Day 1		
200	14	21
500	25	59
1000	43	128
Day 7		
200	19	37
500	32	83
1000	51	143

$AUC_{0\text{-}inf}$ area under the concentration time curve from time 0 to inf; C_{max} maximum concentration; hr hours; NHC EIDD 1931 or N hydroxycytidine; TK toxicokinetic

There were no gender-related differences in Day 7 (or Day 1) plasma levels of NHC. There was a slight increase in exposure on Day 7, which was more pronounced at lower doses: AUC_{Day7}/AUC_{Day1} were 1.1, 1.4, and 1.8 in mice dosed at 1000, 500, and 200 mg/kg, respectively. Therefore, the MTD in this study was 1000 mg/kg/day (Day 7 NHC $AUC_{0\ 24hr}$ 142.35 µM*hr; C_{max} 51.31 µM).

3.1.2 A 28-Day Study in Wild Type CByB6F1 Tg(HRAS)2Jic Mice (TT #[redacted]-9037)

The objective of this study was to determine the potential toxicity of MOV when given orally once daily for 28 days to WT CByB6F1 Tg(HRAS)2Jic mice [Sec. 2.6.7: 7A]. In addition,

the TK characteristics of MOV were determined. The study design is presented in [Table 2.6.6: 3].

Table 2.6.6: 3 Experimental Design – Main and TK (TT #[redacted]-9037)

Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals			
				Main Study		Toxicokinetic Study	
				Males	Females	Males	Females
Control Article[a]	0	10	0	10	10	3	3
MOV	100	10	10	10	10	18	18
MOV	300	10	30	10	10	18	18
MOV	700	10	70	10	10	18	18
MOV	2000	10	200	10	10	18	18

a 1% Methylcellulose (400 cps) in reverse osmosis deionized water.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, and clinical and anatomic pathology evaluations. Plasma MOV concentrations were determined.

There was no mortality. There were no MOV-related clinical signs, and no changes in mean food consumption. There were no MOV-related effects in clinical pathology parameters, organ weights, macroscopic, or microscopic findings.

In male mice, there were decreases in mean body weight gain from Days 1 to 29 at 100 (-28%), 300 (-24%), 700 (-56%), and 2000 (-77%) mg/kg/day compared to controls; the decreases reached statistical significance in the 700 and 2000 mg/kg/day dose groups. In female mice, there were decreases in mean body weight gain at 700 (-30%) and 2000 (-30%) mg/kg/day. There were no decrements in female body weight at 100 or 300 mg/kg/day. There was no associated decrease in mean food consumption.

MOV TK parameters are presented in [Table 2.6.6: 4].

Table 2.6.6: 4 Mean Plasma MOV TK Parameters in Mice Following Oral Dosing of MOV: Study Day 28 (TT #[redacted]-9037)

				Sex					
				Females		Males		Sex-Combined	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE	Mean	SE
100	2	$AUC_{0\text{-}24hr}$	hr*µM	NC[a]	NC[a]	NC[a]	NC[a]	NC[a]	NC[a]
		C_{max}	µM	0.0442	0.00428	0.0331	0.00422	0.0387	0.00366
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
300	3	$AUC_{0\text{-}24hr}$	hr*µM	0.0928	NC	0.109	0.0157	0.107	0.0130
		C_{max}	µM	0.132	NC	0.187	0.0270	0.173	0.0236
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
700	4	$AUC_{0\text{-}24hr}$	hr*µM	NC[b]	NC[b]	0.378	0.0698	0.332	0.0705
		C_{max}	µM	0.225	0.335	0.409	0.0435	0.317	0.0478
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
2000	5	$AUC_{0\text{-}24hr}$	hr*µM	1.38	0.264	NC[b]	NC[b]	1.45	0.221
		C_{max}	µM	0.833	0.243	1.42	0.566	1.12	0.333
		T_{max}	hr	1.00	NC	0.500	NC	0.500	NC

$AUC_{0\text{-}24hr}$ area under the time concentration curve from 0 to 24 hrs; Cmax maximum concentration; hr hour(s); NC not calculated; SE standard error; Tmax time of maximum concentration.

NC[a] Not calculated due to insufficient data MOV concentrations were <LLOQ of the bioanalytical assay after 1 hour postdose

NC[b] Not calculated due to insufficient data volume from some samples not sufficient to complete the concentration analysis

MOV concentrations in plasma from all control group animals were below the lower limit of quantitation of the bioanalytical method.

At doses available for comparison, no sex differences were observed in mean plasma MOV $AUC_{0\ 24hr}$ and C_{max} values; therefore, all results and conclusions for MOV were based upon sex combined data. Mean plasma MOV $AUC_{0\ 24hr}$ values were greater than dose proportional between 300 and 2000 mg/kg/day; while mean plasma MOV C_{max} values were approximately dose proportional between 100 and 2000 mg/kg/day. Due to bioanalytical assay issues, the NHC TK parameters could not be calculated. NHC TK parameters were calculated in a 7-day TK study in WT CByB6F1 Tg(HRAS)2Jic mice conducted at doses of 100, 300, 700, and 2000 mg/kg/day (TT #[redacted]-9011), and are presented in [Sec. 2.6.6: 8.7.2.1].

In conclusion, MOV, administered orally to WT CByB6F1 Tg(HRAS)2Jic mice once daily at doses of 0, 100, 300, 700, or 2000 mg/kg/day for 28 days produced decreases in mean body weight gain in males at all doses, and in females at the 700 and 2000 mg/kg/day doses. Therefore, based on these results, the NOEL was 300 mg/kg/day in females, and was not

established in the males. The NOAEL was 300 mg/kg/day in both sexes (NHC $AUC_{0\ 24hr}$ exposure 1-fold the clinical NHC exposure at 800 mg Q12H, obtained from the 7-day oral gavage TK study in WT CByB6F1 Tg(HRAS)2Jic mice, TT #[redacted]-9011) based on the adverse decreases in body weight gain (which reached at least -30%) at doses ≥700 mg/kg/day.

3.2 Rats

3.2.1 Oral MTD/7-Day Dose-Range-Finding in Rats (TT #[redacted]-7825)

This 2-phase non-GLP study was conducted: (1) to identify the single-dose MTD of MOV when administered to rats once via oral gavage (Phase A); and (2) to characterize the toxicity and TK of MOV and NHC when MOV was administered to rats by oral gavage once daily for up to 7 consecutive days (Phase B) [Sec. 2.6.7: 6] to select doses for a GLP 28-day toxicity and TK study [Sec. 2.6.6: 3.2.2].

In Phase A, a single dose of 500, 1000, 1500, or 2000 mg/kg of MOV was administered to SD rats (2/sex/group). Based on the results of Phase A, animals in Phase B (5/sex/group) received 7 consecutive daily doses of 0, 200, 700, or 2000 mg/kg and were evaluated for standard-in-life parameters followed by complete necropsy with organ weights. No histopathology was conducted. Plasma drug concentrations of MOV and NHC were determined.

No mortality occurred during either phase. During Phase A, the only MOV-related change was a mean body weight loss of several grams for males and females at 2000 mg/kg during the first few days post-treatment, which correlated to 30% respective decreases, in food consumption.

During Phase B, MOV-related clinical signs (soiling, piloerection, unkempt appearance, and evidence of dehydration) occurred near the end of treatment, primarily in the 2000 mg/kg/day males. At the end of Phase B, mean body weight was 15% below controls in high-dose males ($p<0.01$), which corresponded to significant decreases in food consumption for this group. Sporadic, statistically significant decreases in mean food consumption occurred for the 2000 mg/kg/day females during Phase B, with no apparent effect on body weight.

At the end of Phase B, the 2000 mg/kg/day males had several statistically significant changes in hematology parameters compared to controls, most notably decreased (89%) mean RET count. RET counts were also statistically significantly decreased in the high-dose females, but the values remained within the reference range. White blood cell and absolute lymphocyte counts were decreased (52%) for the 2000 mg/kg/day males. Changes in clinical chemistry parameters, included statistically significantly increased ALT (2-fold) and AST (1.86X) for high-dose males and increased ALT (1.63X), calcium (1.10X), glucose (3.4X), and inorganic phosphorus (1.17X) for high-dose females, compared to concurrent controls.

MOV-related macroscopic observations were limited to the stomachs (distended with digesta), with males more affected, and lungs of some males administered 2000 mg/kg/day (mottled lungs or lungs with dark foci). MOV-related organ weight changes occurred in the 2000 mg/kg/day animals and included decreased spleen weights in both sexes with increased

brain, lung, and adrenal gland weights and decreased testes and epididymides weights in males.

Toxicokinetic parameters are presented in [Table 2.6.6: 5] and [Table 2.6.6: 6].

Table 2.6.6: 5 Plasma TK Parameters for NHC after a Single Oral Dose of MOV in Rats (TT #[redacted]-7825)

Dose (mg/kg)	Gender	Tmax (hr)	Cmax (µM)	AUC_{0-24hr} (µM*hr)
200	Male	1	85.8	205
	Female	0.5	90.3	101
700	Male	0.5	369	960
	Female	0.5	414	706
2000	Male	0.5	764	2180
	Female	0.5	696	1271

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; Cmax maximum concentration; hr hours; NHC EIDD 1931 or N hydroxycytidine; TK toxicokinetic; Tmax time to maximum concentration.

Table 2.6.6: 6 Plasma TK Parameters for NHC after 7 Days of Oral Dosing of MOV in Rats (TT #[redacted]-7825)

Dose (mg/kg)	Gender	Tmax (hr)	Cmax (µM)	AUC_{0-24hr} (µM*hr)
200	Male	1	63.2	172
	Female	1	62.1	96
700	Male	1	399	1461
	Female	0.5	209	436
2000	Male	2	916	6917
	Female	2	1057	4642

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; Cmax maximum concentration; hr hour(s); NHC EIDD 1931 or N hydroxycytidine; TK toxicokinetic; Tmax time to maximum concentration.

After single or repeat oral administration of MOV, the prodrug MOV was not detected in plasma of rats dosed at 200 mg/kg but was quantifiable in plasma sporadically at very low levels after doses of 700 and 2000 mg/kg. Following a single dose of MOV, plasma NHC C_{max} and $AUC_{0\ 24hr}$ increased approximately in proportion to dose in both sexes. Following repeated daily administration of MOV for 7 days, plasma NHC C_{max} values increased a little greater than in proportion to dose. Day 7 $AUC_{0\ 24hr}$ values increased greater than in proportion to dose in both males and females. There was no meaningful increase in C_{max} on Day 7 versus Day 1. There was no increase in $AUC_{0\ 24hr}$ on Day 7 versus Day 1 at 200 and 700 mg/kg/day. In rats dosed at 2000 mg/kg/day, Day 7 $AUC_{0\ 24hr}$ was 3.4-fold higher than Day 1 $AUC_{0\ 24hr}$. $AUC_{0\ 24hr}$ in males was 1.4- to 3.4-fold higher than in females; this ratio was not dose dependent.

In conclusion, the dose of 2000 mg/kg/day was associated with clinical signs of toxicity and significantly decreased body weights in males with changes in hematology parameters, including decreased RET counts, white blood cell counts, and absolute lymphocyte counts. High-dose males had clinical chemistry changes that included slightly increased liver enzymes (ALT and AST). High-dose females showed only mild elevations of ALT, calcium, glucose, and inorganic phosphorus. The improved tolerability in females compared to males at 2000 mg/kg/day is likely attributable to 1.4- to 3.4-fold lower exposures in females compared to males.

3.2.2 Oral 28-Day Toxicology and Toxicokinetics in Rats With a 14-Day Recovery (TT #[redacted]-7814)

The objective of this study was to evaluate the potential toxicity of MOV and the TK profile of MOV and NHC, when MOV was administered once daily by oral gavage to rats for 28 days [Sec. 2.6.7: 7B].

Crl:CD(SD) rats were assigned to 4 groups of 15 females and 15 males each that received 50, 150, or 500 mg/kg/day of MOV in 1% methylcellulose in deionized water or vehicle only, at a dose volume of 10 mL/kg. Five rats/sex/group were dedicated to assess reversibility of potential findings during a 14-day recovery phase. Systemic exposure was evaluated in additional satellite TK groups, with 3/sex/group receiving vehicle and 9/sex/group in the MOV treatment groups. The high dose was selected based on the adverse findings noted at 2000 mg/kg/day in the MTD/7-day dose-range-finding study in rats (TT #[redacted]-7825) [Sec. 2.6.6: 3.2.1].

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma drug concentrations of MOV and NHC in treated and control samples were determined. Bone marrow smears were prepared and evaluated.

All animals survived until their scheduled termination, with no MOV-related clinical signs or meaningful changes in body weight or food consumption. There were no test article-related changes in ophthalmic or clinical pathology parameters. Lymphocyte percentages were within expected values for SD rats at 500 mg/kg/day. At the end of the treatment and recovery phases, no changes were noted on evaluation of bone marrow (including myeloid:erythroid ratios) at 500 mg/kg/day.

Test article-related organ weight increases (absolute and relative to body weight and brain weight) occurred in the liver at a dose of 500 mg/kg/day by the end of treatment but were within normal range by the end of the recovery phase. No microscopic correlates were noted in the liver. There were no test article-related clinical pathology, macroscopic, or microscopic findings at the terminal or recovery sacrifice.

MOV and NHC TK parameters are presented in [Table 2.6.6: 7] and [Table 2.6.6: 8].

Table 2.6.6: 7 Mean Plasma MOV TK Parameters in Rats Following Oral Dosing of MOV (TT #[redacted]-7814)

Dose (mg/kg/day)	Day 1 (Female/Male)			Day 28 (Female/Male)		
	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)
50	BLQ/BLQ	ND/ND	ND/ND	BLQ/BLQ	ND/ND	ND/ND
150	BLQ/0.13	ND/0.14	ND/ND	0.21/0.20	0.31/0.38	ND/ND
500	0.92/0.60	0.98/0.61	1.26/0.582	1.01/1.14	1.17/1.55	ND/2.15

AUClast area under the concentration time curve from time 0 through the last measurable concentration; Cmax maximum concentration; hr hour(s); ND not determined; $t_{1/2}$ terminal elimination phase half life; TK toxicokinetic.
MOV concentrations in plasma from all control group animals were below the lower limit of quantitation on Day 1 and Day 28.

Table 2.6.6: 8 Mean Plasma NHC TK Parameters in Rats Following Oral Dosing of MOV (TT #[redacted]-7814)

Dose (mg/kg/day)	Day 1 (Female/Male)			Day 28 (Female/Male)		
	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)
50	3.76/10.96	6.29/22.22	2.04/2.22	6.06/10.49	9.68/20.91	1.65/2.10
150	22.64/44.36	37.15/108.40	1.69/2.58	24.03/52.08	42.43/107.63	1.44/2.45
500	150.84/175.53	269.66/432.07	3.98/ 6.11	181.70/213.33	318.65/590.23	3.36/3.36

AUClast area under the concentration time curve from time 0 through the last measurable concentration; Cmax maximum concentration; hr hour(s); $t_{1/2}$ terminal elimination phase half life; TK toxicokinetic.
NHC concentrations in plasma from all control group animals were below the lower limit of quantitation on Day 1 and Day 28.

No sex differences in plasma MOV TK were observed. However, slight, but consistent sex differences were observed in NHC TK, such that mean plasma NHC AUC_{last} and C_{max} values in males were slightly higher than those in females on Study Days 1 and 28. Following single and multiple oral doses of MOV at 50, 150, and 500 mg/kg/day, MOV levels in rat plasma were low and only observed for a short period. Following single or multiple oral doses of 50, 150, and 500 mg/kg/day of MOV, NHC group peak (C_{max}) and total (AUC_{last}) exposure increased in a greater-than-dose-proportional manner on both Days 1 and 28. Slight-to-no accumulation was observed on Day 28 for NHC compared with Day 1.

In conclusion, MOV was well tolerated when administered to rats at doses of 50, 150, or 500 mg/kg/day for 28 days. The only test article-related finding noted was nonadverse increased liver weights (12-17% in females and males, respectively relative to brain weight) at the end of the treatment phase for the 500 mg/kg/day males and females. Therefore, the NOAEL was ≥500 mg/kg/day (AUC_{last} ~319 [female]/590 [male] µM*hr, 4.2-fold [female] and 7.8-fold [male] the clinical NHC exposure at 800 mg Q12H).

3.2.3 Three-Month Oral Toxicity and Toxicokinetic Study in Rats (TT #[redacted]-1014)

The purpose of this study was to determine the potential toxicity of MOV and the TK profile of MOV and NHC, when MOV was administered once daily by oral gavage to rats for approximately 3 months [Sec. 2.6.7: 7C].

Crl:CD(SD) rats were assigned to 4 groups of 10 females and 10 males each that received 150 (males only), 200 (females only), 500, or 1000 mg/kg/day of MOV in 1% methylcellulose in deionized water or vehicle only, at a dose volume of 10 mL/kg. The high dose was selected based on the adverse findings noted at 2000 mg/kg/day in the MTD/7-day dose-range-finding study in rats (TT #[redacted]-7825) [Sec. 2.6.6: 3.2.1] and the NOAEL of ≥500 mg/kg/day in the 28-day oral toxicology and toxicokinetics in rats with a 14-day recovery (TT #[redacted]-7814) [Sec 2.6.6: 3.2.2].

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma drug concentrations of MOV and NHC in treated and control samples were determined.

There were no unscheduled deaths. There were no test article-related clinical signs or changes in ophthalmic or clinical pathology parameters.

Test article-related antemortem findings were limited to decreases in mean body weight gain in males at 150, 500 and 1000 mg/kg/day and in females at 500 and 1000 mg/kg/day compared to concurrent controls. In Study Week 13, the decreases in males were -13%, -25%, and -55%, respectively, while the decreases in females were -8% and -9%, respectively. The decreases in body weight gain correlated with very slight to slight decreases in weekly mean food consumption in these groups.

Test article-related histomorphologic changes were limited to the growth plate of male rats at 500 and 1000 mg/kg/day, and of female rats at 1000 mg/kg/day; and to the tracheal cartilage of male rats at 500 and 1000 mg/kg/day. Increased thickness of the physis of the long bones (femur and tibia) with decreased osteogenesis, leading to variably decreased trabecular bone in the metaphysis, was observed in male rats dosed at 1000 mg/kg/day. Occasionally, the physeal cartilage was disrupted allowing for the metaphyseal trabecular bone to be displaced towards the epiphysis, which correlated with the gross finding of focally increased thickness of bone. Minimal to mild increase in thickness of the growth cartilage of the epiphysis of long bones and patella, frequently with chondrocytes showing hypereosinophilic cytoplasm within distended lacunae was observed in males and females at 1000 mg/kg/day. Growth plate findings at 500 mg/kg/day were limited to minimal increases in the thickness of the growth cartilage of the epiphysis and patella in males. The remaining tissues in the femorotibial joint, including articular surfaces, ligaments, synovial tissue, and other soft tissue, were unremarkable. The growth plate findings observed in rats are not considered to represent a risk for adult human subjects because physis/epiphysis growth cartilage which was active in growing rats from the 3-month toxicity study is not present in adult humans [Ref. 4.3: 05NK2R].

Minimal to mild eosinophilic cytoplasmic alteration of tracheal chondrocytes associated with altered distribution of the chondrocytes as single and isogenous groups within the matrix was observed in the cartilage of the trachea in male rats dosed at 500 and 1000 mg/kg/day. This change did not impact the overall structure or integrity of the cartilage, did not impact airway size/diameter and was not associated with degenerative or inflammatory changes. The epithelium and the glands within the lamina propria of the trachea were also not remarkable. Based on these findings, this cytoplasmic alteration of tracheal chondrocytes was nonadverse.

In addition, organ weight and histomorphologic changes that were considered secondary to decreased body weight gain and not primary MOV-related changes were observed in multiple tissues in male rats dosed at 1000 mg/kg/day.

The TK parameters are presented in [Table 2.6.6: 9] through [Table 2.6.6: 12].

Table 2.6.6: 9 Mean Plasma MOV TK Parameters in Rats Following Oral Dosing of MOV: Study Week 2 (TT #[redacted]-1014)

				Sex					
				Female		Male		Sex-Combined	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE	Mean	SE
150	2	$AUC_{0\ 24hr}$	hr*µM	NA	NA	0.332	0.0358	NA	NA
		C_{max}	µM	NA	NA	0.171	0.0197	NA	NA
		T_{max}	hr	NA	NA	0.500	NC	NA	NA
200	3	$AUC_{0\ 24hr}$	hr*µM	0.443	0.0464	NA	NA	NA	NA
		C_{max}	µM	0.270	0.0143	NA	NA	NA	NA
		T_{max}	hr	0.500	NC	NA	NA	NA	NA
500	4	$AUC_{0\ 24hr}$	hr*µM	1.07	0.0991	1.33	0.101	1.20	0.0937
		C_{max}	µM	0.569	0.0237	0.487	0.0788	0.528	0.0411
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
1000	5	$AUC_{0\ 24hr}$	hr*µM	3.29	0.438	4.32	0.534	3.80	0.355
		C_{max}	µM	1.50	0.365	1.43	0.250	1.46	0.199
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC

$AUC_{0\text{-}24hr}$ area under the time concentration curve from 0 to 24 hrs; Cmax maximum concentration; hr hour(s); NA Not Applicable; NC not calculated; SE standard error; Tmax time of maximum concentration.

MOV concentrations in plasma from all control group animals at 0.5 hour were below the lower limit of quantitation of the bioanalytical method in Study Week 2

Table 2.6.6: 10 Mean Plasma NHC TK Parameters in Rats Following Oral Dosing of MOV: Study Week 2 (TT #[redacted]-1014)

				Sex			
				Female		Male	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE
150	2	$AUC_{0\text{-}24hr}$	hr*µM	NA	NA	75.3	2.82
		C_{max}	µM	NA	NA	27.5	3.34
		T_{max}	hr	NA	NA	1.00	NC
200	3	$AUC_{0\text{-}24hr}$	hr*µM	108	10.9	NA	NA
		C_{max}	µM	63.4	16.9	NA	NA
		T_{max}	hr	0.500	NC	NA	NA
500	4	$AUC_{0\text{-}24hr}$	hr*µM	251	21.1	362	24.5
		C_{max}	µM	97.5	6.85	140	16.6
		T_{max}	hr	1.00	NC	1.00	NC
1000	5	$AUC_{0\text{-}24hr}$	hr*µM	660	70.2	1,280	141
		C_{max}	µM	265	7.89	260	19.6
		T_{max}	hr	1.00	NC	1.00	NC

$AUC_{0\text{-}24hr}$ area under the time concentration curve from 0 to 24 hrs; Cmax maximum concentration; hr hour(s); NA Not Applicable; NC not calculated; SE standard error; Tmax time of maximum concentration.

NHC concentrations in plasma from all control group animals at 0.5 hour were below the lower limit of quantitation of the bioanalytical method in Study Week 2.

Table 2.6.6: 11 Mean Plasma MOV TK Parameters in Rats Following Oral Dosing of MOV: Study Week 13 (TT #[redacted]-1014)

				Sex					
				Female		Male		Sex-Combined	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE	Mean	SE
150	2	$AUC_{0\ 24hr}$	hr*µM	NA	NA	0.557	0.0499	NA	NA
		C_{max}	µM	NA	NA	0.402	0.0290	NA	NA
		T_{max}	hr	NA	NA	0.500	NC	NA	NA
200	3	$AUC_{0\ 24hr}$	hr*µM	0.755	0.0816	NA	NA	NA	NA
		C_{max}	µM	0.605	0.0685	NA	NA	NA	NA
		T_{max}	hr	0.500	NC	NA	NA	NA	NA
500	4	$AUC_{0\ 24hr}$	hr*µM	2.63	0.510	2.32	0.305	2.48	0.278
		C_{max}	µM	1.29	0.199	0.966	0.206	1.13	0.147
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
1000	5	$AUC_{0\ 24hr}$	hr*µM	4.43	0.862	5.67	0.594	5.19	0.650
		C_{max}	µM	2.15	0.231	1.79	0.0994	1.95	0.215
		T_{max}	hr	0.500	NC	2.00	NC	0.500	NC

$AUC_{0\text{-}24hr}$ area under the time concentration curve from 0 to 24 hrs; Cmax maximum concentration; hr hour(s); NA Not Applicable; NC not calculated; SE standard error; Tmax time of maximum concentration.

MOV concentrations in plasma from all control group animals were above the lower limit of quantitation of the bioanalytical method in Study Week 13. These values were approximately 5.6% or less of the mean C_{max} value of the low dose group.

Table 2.6.6: 12 Mean Plasma NHC TK Parameters in Rats Following Oral Dosing of MOV: Study Week 13 (TT #[redacted]-1014)

				Sex			
				Female		Male	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE
150	2	$AUC_{0\text{-}24hr}$	hr*µM	NA	NA	52.2	9.85
		C_{max}	µM	NA	NA	15.6	4.80
		T_{max}	hr	NA	NA	2.00	NC
200	3	$AUC_{0\text{-}24hr}$	hr*µM	67.6	9.09	NA	NA
		C_{max}	µM	57.2	12.3	NA	NA
		T_{max}	hr	0.500	NC	NA	NA
500	4	$AUC_{0\text{-}24hr}$	hr*µM	250	22.3	408	24.9
		C_{max}	µM	161	43.0	148	12.5
		T_{max}	hr	0.500	NC	1.00	NC
1000	5	$AUC_{0\text{-}24hr}$	hr*µM	706	166	1,120	81.3
		C_{max}	µM	301	64.5	279	20.3
		T_{max}	hr	0.500	NC	1.00	NC

$AUC_{0\text{-}24hr}$ area under the time concentration curve from 0 to 24 hrs; Cmax maximum concentration; hr hour(s); NA Not Applicable; NC not calculated; SE standard error; Tmax time of maximum concentration.

NHC concentrations in plasma from all control group animals at 0.5 hour were below the lower limit of quantitation of the bioanalytical method in Study Week 13.

No sex differences in plasma MOV TK were observed. However, slight, but consistent, sex differences were observed in NHC TK, such that mean plasma NHC $AUC_{0\ 24hr}$ values in males were slightly higher than those in females in Study Weeks 2 and 13; and mean plasma NHC C_{max} was slightly higher in males than in females at 500 mg/kg/day in Study Week 2 (otherwise, mean NHC C_{max} values were generally similar in males and females at other doses and TK periods).

In Study Week 2, mean plasma MOV $AUC_{0\ 24hr}$ values were approximately dose proportional between 150 (males only) or 200 (females only) and 500 mg/kg/day (sex-combined), but mean sex-combined plasma MOV $AUC_{0\ 24hr}$ values were greater than dose proportional between 500 to 1000 mg/kg/day. Mean plasma MOV C_{max} values were approximately dose proportional between 150 (males), 200 (females) and 1000 mg/kg/day (sex-combined). In Study Week 13, mean plasma MOV $AUC_{0\ 24hr}$ values were greater than dose proportional between 150 (males only) or 200 mg/kg/day (females only) and 500 mg/kg/day (sex-combined), but were approximately dose proportional between 500 and 1000 mg/kg/day (sex-combined). Mean plasma MOV C_{max} values were approximately dose

proportional between 150 (males only) or 200 mg/kg/day (females only) and 1000 mg/kg/day (sex-combined).

In Study Week 2, mean plasma NHC $AUC_{0\ 24hr}$ values in males were greater than dose proportional between 150 and 1000 mg/kg/day; mean plasma C_{max} values were greater than dose proportional between 150 and 500 mg/kg/day, and approximately dose proportional between 500 and 1000 mg/kg/day. In females, mean plasma NHC $AUC_{0\ 24hr}$ was approximately dose proportional between 200 and 500 mg/kg/day, and slightly greater than dose proportional between 500 and 1000 mg/kg/day; mean plasma NHC C_{max} in females was slightly less than dose proportional between 200 and 500 mg/kg/day, and slightly greater than dose proportional between 500 and 1000 mg/kg/day. In Study Week 13, mean plasma NHC $AUC_{0\ 24hr}$ value in males and females were greater than dose proportional between 150 and 1000 mg/kg/day (males), and between 200 and 1000 mg/kg/day (females). Mean plasma NHC C_{max} in males was greater than dose proportional between 150 and 500 mg/kg/day, and approximately dose proportional between 500 and 1000 mg/kg/day. Mean plasma NHC C_{max} in females was approximately dose proportional between 200 and 1000 mg/kg/day.

After repeated daily dosing of MOV, mean plasma MOV $AUC_{0\ 24hr}$ and C_{max} values in Study Week 13 were consistently slightly to moderately higher than those achieved in Study Week2. Mean plasma NHC $AUC_{0\ 24hr}$ values at 150 mg/kg/day in males and 200 mg/kg/day in females in Study Week 13 were slightly lower than those achieved in Study Week 2, while mean plasma NHC $AUC_{0\ 24hr}$ values at 500 and 1000 mg/kg/day in Study Week 13 were similar to those achieved in Study Week 2. Mean plasma NHC C_{max} values in males and females in Study Week 13 were generally similar to those achieved in Study Week 2; except at 150 mg/kg/day in males, when the mean plasma NHC C_{max} value in Study Week 13 was slightly lower than that obtained in Study Week 2; and at 500 mg/kg/day in females, when the mean plasma NHC C_{max} value in Study Week 13 was slightly higher than that obtained in Study Week 2. In Study Weeks 2 and 13, mean plasma NHC $AUC_{0\ 24hr}$ and C_{max} values were substantially higher than those obtained for plasma MOV.

Based on these findings, the NOEL was <150 mg/kg/day for males and 200 mg/kg/day for females. Based on adverse findings in growth plate in males (in addition to the notable decreased body weight gain) at ≥500 mg/kg/day and in females at 1000 mg/kg/day, the NOAELs were 150 mg/kg/day in males ($AUC_{0\ 24hr}$ of 52.2 µM*hr, 0.7-fold the clinical NHC exposure at 800 mg Q12H) and 500 mg/kg/day in females ($AUC_{0\ 24hr}$ of 250 µM*hr, 3.3-fold the clinical NHC exposure at 800 mg Q12H).

3.3 Dogs

3.3.1 Oral MTD/7-Day Dose-Range-Finding in Dogs (TT # [redacted]-7826)

This 2-phase non-GLP study was conducted: (1) to identify the single-dose MTD of MOV when administered to dogs once via oral gavage (Phase A); and (2) to characterize the toxicity and TK of MOV and NHC when MOV was administered to dogs by oral gavage once daily for up to 7 consecutive days (Phase B) [Sec. 2.6.7: 6] to select doses for a GLP 28-day toxicity and TK study [Sec. 2.6.6: 3.3.2]. In Phase A, a single dose of 300, 500, 1000, or 2000 mg/kg was administered to beagle dogs (1/sex/group). Based on the Phase A results,

animals in Phase B (2/sex/group) received up to 7 consecutive daily doses of 0, 100, 300, or 1000 mg/kg/day and were evaluated for standard in-life and post-life parameters, except histopathology was not performed.

During Phase A, no mortality occurred and clinical signs were limited to minimal, transient GI effects, including emesis and soft feces at ≥300 mg/kg. All Phase A animals lost weight by Day 3, which corresponded to decreases in food consumption.

During Phase B, 1 male administered 1000 mg/kg/day was euthanized on Day 4 due to marked clinical signs of toxicity (recumbency, pale mucous membranes, ulceration in the oral cavity, black tarry stool, tachycardia, and other indicators of shock). Surviving high-dose dogs were also necropsied on Day 4. Terminal necropsy for the 300 mg/kg/day animals was moved to Day 7 because similar clinical signs of poor and deteriorating physical condition began to manifest in the mid-dose animals at this time. Control and low-dose animals were euthanized as scheduled on Day 8. In general, test article-related changes during Phase B (including decreased activity, emesis, diarrhea, and partial eyelid closure) were observed in males administered ≥300 mg/kg/day and in all MOV female groups. Progressive, dose-responsive mean body weight loss, compared to pretreatment weights, typically occurred by Day 4 in dogs administered ≥300 mg/kg/day and by Day 5 in the 100 mg/kg/day groups with correlative decreases in food consumption. Changes in hematology were limited to marked decreases in absolute lymphocyte counts in dogs administered ≥300 mg/kg/day (likely secondary to glucocorticoid response (stress) associated with severity of clinical signs at this non-tolerated dose). Multiple, dose-responsive changes in the clinical chemistry parameters, relative to standard reference ranges, occurred at doses ≥300 mg/kg/day. These changes included increases in AST (up to 30-fold at 1000 mg/kg/day; 2-fold at 300 mg/kg/day) as well as increased ALP, ALT (up to 5-fold at 1000 mg/kg/day only), total cholesterol, and triglycerides, with decreased potassium (K), chloride (Cl), and calcium (Ca).

Macroscopic observations occurred in all MOV-treated groups and were primarily associated with the GI tract (including the mouth, esophagus, and large and small intestines). These observations included the presence of red and/or darkened foci, discolored mucosa (dark, red, and/or green), and thickened mucosa. Dose-responsive, organ weight changes were noted most often in the reproductive organs as well as in the liver, spleen, and thymus of animals administered ≥300 mg/kg/day.

TK parameters are presented in [Table 2.6.6: 13] and [Table 2.6.6: 14].

Table 2.6.6: 13 Plasma TK Parameters for MOV and NHC after a Single Oral Dose of MOV in Dogs (TT #[redacted]-7826)

Dose (mg/kg)	Analyte	t1/2 (hr)	Tmax (hr)	Cmax (µM)	AUCinf (µM*hr)
100	MOV	0.2	0.5	11.8	6.7
300	MOV	0.9	0.5	43.4	26.7
1000	MOV	0.5	0.5	118	103
100	NHC	6.2	0.6	220	501
300	NHC	4.6	0.6	694	1697
1000	NHC	4.9	0.9	1300	5011

AUCinf area under the time concentration curve extrapolated to infinity; Cmax maximum concentration; hr hour(s); N Number; t1/2 terminal half life; TK Toxicokinetic; Tmax time of maximum concentration.

Table 2.6.6: 14 Plasma TK Parameters for MOV and NHC after Multiple Oral Doses of MOV in Dogs (TT #[redacted]-7826)

Dose (mg/kg)	Analyte	t1/2 (hr)	Tmax (hr)	Cmax (µM)	$AUC_{0\text{-}24hr}$ (µM*hr)
100	MOV	0.2	0.5	19.4	11.8
300[a]	MOV	0.6	0.5	68.3	70.5
100	NHC	5.7	0.9	239	637
300[a]	NHC	5.8	0.8	401	1431

$AUC_{0\text{-}24hr}$ area under the time concentration curve from 0 to 24 hrs; Cmax maximum concentration; hr hour(s); N Number; t1/2 terminal half life; TK Toxicokinetic; Tmax time of maximum concentration.

[a] N 3; one dog had emesis 6 minutes after the dose and was excluded from calculations.

There were no meaningful differences in male and female TK parameters for NHC or MOV in dogs at any dose after single or repeated administration, and TK parameters were combined. AUC_{inf} and $AUC_{0\ 24hr}$ on Day 1 and Day 6 were dose dependent and approximately proportional at all doses. No accumulation of NHC occurred after daily dosing at 100 or 300 mg/kg/day.

In conclusion, MOV was tolerated in dogs administered a single dose of up to 2000 mg/kg. In the repeat-dose phase, the doses of 300 and 1000 mg/kg/day exceeded the MTD due to mortality, clinical signs of toxicity and adverse clinical pathology changes noted at these doses. Body weight loss was observed at 100 mg/kg/day beginning Day 5.

3.3.2 Oral 28-Day Toxicology and Toxicokinetics in Dogs with a 28-Day Recovery (TT [redacted]-7815)

The objective of this study was to evaluate potential toxicity of MOV and the TK profile of MOV and NHC, when MOV was administered once daily by oral gavage to dogs for 28 days [Sec. 2.6.7: 7D].

Beagle dogs were assigned to 4 groups of 5 females and 5 males each that received 6, 17, or 50 mg/kg/day of MOV in 1% methylcellulose in deionized water or vehicle only, at a dose volume of 2 mL/kg. Two dogs/sex/group were dedicated to assess reversibility of potential findings during a 28-day recovery phase. The high dose was selected based on the body weight loss noted at 100 mg/kg/day in the MTD/7-day dose-range-finding study in dogs (TT #[redacted]-7826) [Sec. 2.6.6: 3.3.1].

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic and ECG examinations, and clinical and anatomic pathology evaluations. Plasma drug concentrations of MOV and NHC in treated and control samples were determined.

Due primarily to marked weight loss, prolonged inappetence, and/or marked hematology findings, the treatment phase for animals given 17 or 50 mg/kg/day was terminated early. Animals at 50 mg/kg/day received their last dose on Day 12 or 14, while animals at 17 mg/kg/day received their last dose on Day 21 (males) or 22 (females). Animals from the main phase were necropsied on the day following the last dose. Recovery necropsies for animals dosed with 50 mg/kg/day (2/sex/group) were performed on Study Day 23/24, whereas recovery animals at 17 mg/kg/day were necropsied at the end of the 28-day recovery phase for the study. Animals in the control and low-dose groups received the intended 28 doses and were necropsied after the treatment phase (3/sex/group) or at the end of the 28-day recovery phase (2/sex/group).

Notable MOV-related clinical signs of toxicity were limited to the 17 and 50 mg/kg/day groups and included red or black feces, decreased activity, and red areas and/or mild hemorrhaging of the oral mucosa. Body weight losses occurred primarily in the 50 mg/kg/day group during treatment. High-dose recovery animals began to gain weight during their brief recovery periods (8 to 11 days). Correlative decreases in individual food consumption (considered as ≤25% consumed) occurred in the 50 mg/kg/day group. In general, for the 50 mg/kg/day males and females, individual food consumption began to decrease during the first week of treatment. Food consumption generally increased for the 50 mg/kg/day dogs when taken off treatment until their necropsy.

No MOV-related effects were noted on ophthalmic parameters or on ECG rhythm, morphology, or quantitative measurements in male or female dogs postdose on Day 1, or following repeat dosing of 6 mg/kg/day during the last week of treatment (Day 28).

The most extensive test article-related gross findings at both the terminal and recovery necropsies were in males at 50 mg/kg/day and primarily consisted of red discoloration of several tissues, including different regions of the digestive tract (from oral mucosa and

esophagus to large intestine) and in urinary bladder, gallbladder, or mediastinal tissue (among other tissues) in individual male dogs. The red discolorations were attributable to hemorrhage and were most likely the result of severe thrombocytopenia observed at ≥17 mg/kg/day in males and females (described below). Similar GI changes occurred in 1 female dosed with 50 mg/kg/day at terminal necropsy only. Discolorations (red/dark involving fewer tissues) were also present in both sexes in terminal animals dosed at 17 mg/kg/day. Most of the gross observations microscopically corresponded to hemorrhage. With the exception of 1 high-dose male with an oral ulcer, the areas of mucosal hemorrhage had histologically normal overlying epithelium, further supporting the assumption that the hemorrhages were likely secondary to extremely low (<14,000 × 10^3 cells/µL) platelet counts observed in animals dosed at ≥17 mg/kg/day.

Adverse histomorphological hematopoietic changes affecting all hematopoietic cell lines and causing subsequent hematological abnormalities (including total WBC count, lymphocytes, neutrophils, reticulocytes, RBCs and platelets) occurred at doses ≥17 mg/kg/day with minor, nonadverse hematological changes at 6 mg/kg/day. The changes were relatively mild at Day 7 and more severe hematologic changes were not apparent until after 14 to 21 days of continuous dosing. The hematopoietic changes were partially reversible or fully reversible following the ~1-week (for the 50 mg/kg/day group) or at least 1-month (for the 17 mg/kg/day group) recovery period, respectively (with essentially normal hematology values after a longer recovery period at doses ≤17 mg/kg/day). Focal hemorrhages (mostly minimal) observed following the dosing period in several animals at ≥17 mg/kg/day (most prominently in the GI tract) were secondary to severe thrombocytopenia. An erosion/ulcer was observed in the buccal mucosa and esophagus in a single male at 50 mg/kg/day. At recovery necropsy, some GI discoloration (reddening) was still present, predominantly in the large intestines, of animals dosed at 50 mg/kg/day, likely attributable to the short recovery period relative to other dose groups.

MOV and NHC TK parameters are presented in [Table 2.6.6: 15] and [Table 2.6.6: 16].

Table 2.6.6: 15 Mean Plasma MOV TK Parameters in Dogs Following Oral Dosing of MOV (TT #[redacted]-7815)

Dose (mg/kg/day)	Day 1 (Female/Male)			Day 28 (Female/Male)		
	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)
6	0.47/0.61	ND/0.56	ND/1.18	0.46/0.38	ND/ND	ND/ND
17	2.02/2.88	0.68/2.96	ND/ND	Euth/Euth	Euth/Euth	Euth/Euth
50	7.83/8.38	6.89/5.34	0.853/1.87	Euth/Euth	Euth/Euth	Euth/Euth

AUClast area under the concentration time curve from time 0 through the last measurable concentration; Cmax maximum concentration; Euth euthanized (no data available); hr hour(s); ND not determined; $t_{1/2}$ terminal elimination phase half life; TK toxicokinetic.

Table 2.6.6: 16 Mean Plasma NHC TK Parameters in Dogs Following Oral Dosing of MOV (TT #[redacted]-7815)

Dose (mg/kg/day)	Day 1 (Female/Male)			Day 28 (Female/Male)		
	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)	Cmax (µM)	AUClast (µM*hr)	$t_{1/2}$ (hr)
6	5.83/4.82	7.48/6.91	2.51/1.08	6.29/6.29	9.41/9.64	4.26/9.05
17	17.67/15.43	30.86/28.43	9.09/7.74	Euth/Euth	Euth/Euth	Euth/Euth
50	50.15/54.01	126.92/110.72	6.26/8.38	Euth/Euth	Euth/Euth	Euth/Euth

AUClast area under the concentration time curve from time 0 through the last measurable concentration; Cmax maximum concentration; Euth euthanized (no data available); hr hour(s); NHC EIDD 1931 or N hydroxycytidine; $t_{1/2}$ terminal elimination phase half life; TK toxicokinetic.

There were no meaningful differences in male and female TK parameters for NHC or MOV in dogs at any dose after single or repeated administration. Following single and multiple doses, MOV levels in dog plasma were low and quantifiable only through 1 to 2 hours postdose, resulting in mostly incomplete TK characterization. However, the NHC group peak exposure (C_{max}) increased in a generally dose-proportional manner and total (AUC_{last}) exposure increased in a greater-than-dose-proportional manner for males and females on Day 1. No or little accumulation was observed on Day 28 (or at dose group termination) for NHC at all doses.

In conclusion, the NOAEL and MTD for this study was 6 mg/kg/day (AUC_{last} 9.53 µM*hr, 0.13-fold the clinical NHC exposure at 800 mg Q12H) primarily due to adverse hematopoietic toxicity that affected all hematopoietic cell lines at ≥17 mg/kg/day (AUC_{last} of ~30 µM*hr [Day 1], 0.4-fold the clinical NHC exposure at 800 mg Q12H). Hematologic changes were relatively mild at Day 7 with more severe changes apparent after 14 to 21 days of continuous dosing. The hematopoietic changes were partially reversible following the ~1 week recovery period for the 50 mg/kg/day group, or fully reversible following the ~1 month recovery period for the 17 mg/kg/day group.

4 GENOTOXICITY

The mutagenic and genotoxic potential of MOV was comprehensively assessed in standard and follow-up regulatory in vitro and in vivo assays designed to detect potential effects on genes (ie, mutations); the overall conclusion was that MOV was not mutagenic or genotoxic in vivo. MOV and NHC induced mutations in the bacterial reverse mutation assay (TT #[redacted]-7810, [Sec. 2.6.7: 8B] and TT #[redacted]-7851, [Sec. 2.6.7: 8A]). MOV did not induce chromosome damage in in vitro or in vivo assays (TT #[redacted]-7806, [Sec. 2.6.7: 8C] and TT #[redacted]-7816, [Sec. 2.6.7: 9A]). Consistent with current regulatory guidances (ICH S2[R1], ICH M7[R1], WHO/IPCS) which recommend follow-up in vivo testing to address the biological/in vivo relevance of in vitro positive results; two robust in vivo mutagenicity studies were performed in rats to understand the in vivo relevance of in vitro positive mutagenicity assays. Both Pig-a mutagenicity (TT #[redacted]-7808, [Sec. 2.6.7: 9B]) and Big Blue® (cII Locus) transgenic (TT #[redacted]-9025, [Sec. 2.6.7: 9C]) rodent assays were conducted per recommended guidelines by international groups [Ref. 4.3: 05RB64, 07WXW2, 07WXX2] and OECD TG 488

[Ref. 4.3: 07WXW5], respectively. These assays included evaluation of standard tissues/cell populations including bone marrow (rapid proliferating tissue) and liver (slow proliferating tissue; high metabolizing capacity) for the Big Blue® (cII Locus) transgenic rodent assay, and reticulocytes and red blood cells for the Pig-a mutagenicity assay. The animals were administered MOV at doses up to the maximum tolerated dose, 500 mg/kg/day, and for longer durations (28 days) than the proposed 5-day clinical administration of MOV in humans. The negative results of these in vivo mutagenicity assays provide strong evidence that the in vitro mutagenicity is not relevant to in vivo mammalian systems. Potential reasons for lack of translation of in vitro findings to in vivo mammalian systems include differences in metabolism, pharmacokinetics, exposure, replication, and DNA repair processes within a whole animal model compared with in vitro test conditions.

4.1 In Vitro

4.1.1 Bacterial Reverse Mutation Assay (TT #[redacted]-7851) (Non-GLP)

This study [Sec. 2.6.7: 8A] evaluated the potential of NHC to induce reverse mutations at loci of TA98, TA100, TA1535, and TA1537 strains of *Salmonella typhimurium* and WP2 *uvrA* strain of *Escherichia coli* in the presence and absence of an exogenous metabolic activation system (S9) [Table 2.6.6: 17].

Table 2.6.6: 17 Precipitate and Toxicity Results (Non-GLP) Bacterial Reverse Mutation Assay (TT #[redacted]-7851)

Tester Strains	Without Metabolic Activation (µg/plate)		With Metabolic Activation (µg/plate)	
	Precipitate	Toxicity[a]	Precipitate	Toxicity
TA98	None	≥500	None	≥1500
TA100	None	≥500	None	≥1500
TA1535	None	≥1500	None	≥1500
TA1537	None	≥500	None	≥1500
WP2 *uvrA*	None	None	None	None

[a] Toxicity is defined as at least moderately reduced background lawn or 50% reduction in revertants compared to negative controls.

Under the conditions of this study, NHC was positive in *Escherichia coli* strain WP2 *uvrA* with and without metabolic activation at concentrations ≥5 µg/plate, and negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without activation.

4.1.2 Bacterial Reverse Mutation Assay (TT #[redacted]-7810) (GLP)

MOV was evaluated for mutagenic activity in the in vitro bacterial reverse mutation assay [Sec. 2.6.7: 8B]. Five tester strains of *Salmonella typhimurium* (TA1537, TA98, TA100, TA102, and TA1535) and *Escherichia coli* strain (WP2 *uvrA*) were used for mutagenicity

testing. MOV was prepared as a stock formulation in dimethylsulfoxide at concentrations up to 50 mg/mL for each assay. Mutagenicity testing was performed in triplicate at each concentration with and without an Aroclor™ 1254-induced rat liver S9 metabolic activation system.

Based on the results of a range-finding assay, MOV was tested in the mutagenicity assay at concentrations of 25.0, 50.0, 100, 250, 500, 1000, 2500, and 5000 µg/plate in triplicate in strains WP2 *uvrA* and TA102 (with and without S9); 1.0, 2.5, 5.0, 10.0, 25.0, 50.0, 100, 250, 500, and 1000 µg/plate in strains TA1537, TA98, TA100, and TA1535 with S9; and 50.0, 100, 250, 500, 1000, 2500, and 5000 µg/plate in strains TA1537, TA98, TA100, and TA1535 without S9 using the plate incorporation method. Precipitates were not observed in any strain either with or without metabolic activation. Cytotoxicity (i.e., reduction in the background lawn and/or mean number of revertant colonies) was observed at 100 µg/plate in TA1537 with metabolic activation; at ≥500 µg/plate in TA1537 and TA100 with metabolic activation; and at 1000 µg/plate in TA98 with metabolic activation.

Increases in the number of revertant colonies as compared with the vehicle control were observed at ≥25.0 µg/plate in TA102 and WP2 *uvrA* strains with metabolic activation; at ≥500 µg/plate in WP2 *uvrA* strain without metabolic activation; and at ≥1000 µg/plate in TA102 strain without metabolic activation. Therefore, a follow-up phenotype test was conducted.

For the phenotype testing, 50 to 100 colonies were restreaked from the mutagenicity plates of strains TA102 (5000 µg/plate without metabolic activation and 100 µg/plate with metabolic activation) and WP2 *uvrA* (5000 µg/plate with and without metabolic activation) onto minimal glucose plates with biotin. Additionally, the same colonies were restreaked onto control nutrient agar plates. The control plates were used to demonstrate that with the presence of histidine and tryptophan that the colonies would grow (both true revertants and phenocopies) and demonstrate that the strains still exhibit normal growth patterns. For both strains with and without metabolic activation, ≥95% colony growth was observed on the streaked minimal glucose plates with biotin and nutrient agar plates, therefore confirming that all colonies are true revertants.

Overall, criteria for a negative response were met for strains TA1537, TA98, TA100, and TA1535 with and without metabolic activation and criteria for a positive response were met for strains TA102 and WP2 *uvrA*, both with and without metabolic activation. The data from the vehicle and positive controls demonstrated the validity and sensitivity of this test system for detecting chemical mutagens with and without metabolic activation.

The mechanism underlying the positive bacterial mutagenicity result is likely to be a result of incorporation into the bacterial DNA. Follow-up studies in two distinct rodent mutagenicity models confirmed a lack of translation of bacterial mutagenicity to in vivo models [Sec. 2.6.6: 4.2.2] and [Sec. 2.6.6: 4.2.3]. The lack of a mutagenic effect in vivo may relate to differences in metabolism, pharmacokinetics, exposure, replication, and DNA repair processes within in vivo mammalian models compared with in vitro test conditions [Ref. 4.3: 05JRSC], [Ref. 4.3: 05JRRY].

4.1.3 In Vitro Micronucleus Assay (TT #[redacted]-7806)

MOV was evaluated for the potential to induce micronuclei in TK6 cells during short (4-hour) and long (27-hour) incubations with or without an exogenous metabolic activation system [Sec. 2.6.7: 8C]. TK6 cultures were treated with the test article, positive control or vehicle control in the presence and absence of an Aroclor™ 1254-induced rat liver S9 microsomal fraction. For the 4-hour treatment without activation micronucleus assay, the concentrations selected for micronucleus analysis were as follows (with percent cytotoxicity): 82.5 µg/mL (12%), 165 µg/mL (18%), and 330 µg/mL (23%). For the 27-hour treatment without activation micronucleus assay, the concentrations selected for micronucleus analysis were as follows (with percent cytotoxicity): 2.58 µg/mL (0%), 61.9 µg/mL (26%), and 248 µg/mL (58%). For the 4-hour treatment with activation micronucleus assay, the concentrations selected for micronucleus analysis were as follows (with percent cytotoxicity): 2.58 µg/mL (2%), 20.6 µg/mL (28%), and 124 µg/mL (56%). Micronuclei were evaluated in 2000 cells per concentration. No statistically significant increases in the percent of micronucleated cells were noted between test article-treated cultures and the concurrent vehicle control under any assay condition.

The percent of micronucleated cells in vehicle and positive control cultures were comparable to the respective historical control data. MOV was negative for inducing micronuclei in TK6 cells in the 4-hour treatments with and without metabolic activation and in the 27-hour treatment without metabolic activation under the conditions of this test system. The percent of micronucleated cells in vehicle and positive control cultures were comparable to the respective historical control data.

4.2 In Vivo

4.2.1 In Vivo Micronucleus Assay of MOV by Oral Gavage in Sprague-Dawley Rats (TT #[redacted]-7816)

The objective of this study [Sec. 2.6.7: 9A] was to assess the potential of MOV to induce micronuclei in polychromatic erythrocytes in rat bone marrow following 2 consecutive days of treatment when given by oral gavage to SD rats at doses of 500, 1000, or 2000 mg/kg/day [Table 2.6.6: 18].

Table 2.6.6: 18 Experimental Design (TT #[redacted]-7816)

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	No. of Animals[b,c]	
					Definitive Phase	
					Males	Females
1	Vehicle (1% methylcellulose)	0	28.6	0	6	6
2	MOV	500	28.6	17.5	6	6
3	MOV	1000	28.6	35	6	6
4	MOV	2000	28.6	70	6	6
5	Positive Control[d]	60	10	6	6	6

[a] Based on the most recent body weight measurement The first day of dosing will be based on Day 1 body weights.

[b] Surviving animals terminated 18 24 hours following the last dose for the vehicle and test article treated groups and at approximately 24 hours following the last dose for the positive control article treated group for bone marrow collection.

[c] The first 5 surviving animals were utilized for bone marrow collection. If not needed, the sixth animal was euthanized via carbon dioxide inhalation without bone marrow collection and discarded.

[d] The positive control article, cyclophosphamide monohydrate, was administered once to animals in Group 5 on Day 2.

Results from this study indicate that MOV did not produce statistically significant or dose-dependent increases in the %MN-PCEs in male or female rats at any dose level compared to the vehicle controls. No bone marrow cytotoxicity (decreases in PCE:TE ratios) was noted in any male or female rats at any MOV dose level. Group mean values for %MN-PCEs and PCE:TE ratios for the vehicle and positive controls were comparable to the 95% historical control intervals obtained by [redacted], demonstrating the acceptability of the assay.

Therefore, MOV was negative for clastogenic activity and/or disruption of the mitotic apparatus under the conditions of this assay.

4.2.2 In Vivo Mammalian Peripheral Blood Erythrocyte Pig-a Mutation Assay in Rat (TT #[redacted]-7808)

The objective of this study [Sec. 2.6.7: 9B] was to determine the potential mutagenicity of MOV, when given by daily oral gavage for 28 days to SD rats using the phosphatidyl inositol glycan class A gene (Pig-a) mutation assay on circulating blood erythrocytes, and to better understand if the mutation effects observed in bacteria [Sec. 2.6.6: 4.1.1], [Sec. 2.6.6: 4.2.2] are relevant in a whole animal mammalian system. The study design is presented in [Table 2.6.6: 19].

Table 2.6.6: 19 Experimental Design (TT #[redacted]-7808)

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals Main Study Males
1	Vehicle Control	0	10	0	6
2	MOV	50	10	5	6
3	MOV	150	10	15	6
4	MOV	500[a]	10	50	6
5	Positive Control	20	10	2	4

[a] Doses higher than 500 mg/kg/day produced notable effects on body weight gain in SD rats. This dose was associated with NHC $AUC_{0\text{-}24hr}$ and C_{max} exposure higher than the human NHC $AUC_{0\text{-}24hr}$ and Cmax exposure, based on toxicokinetic measurements from the from Oral 28 Day Toxicology and Toxicokinetics in Rats With a 14 Day Recovery (TT #[redacted] 7814).

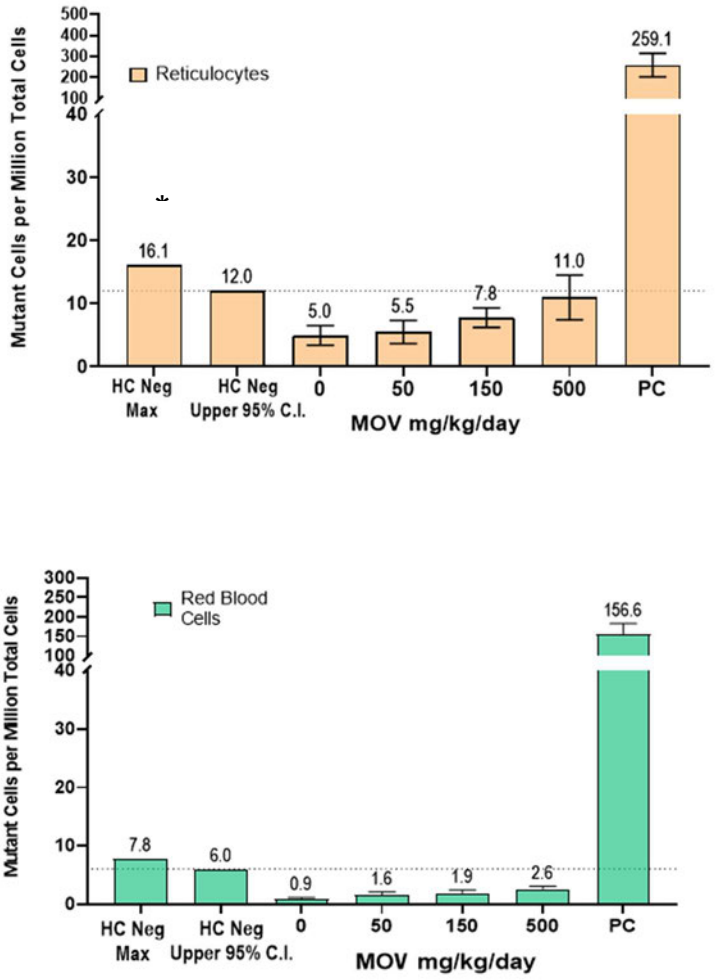
No mortalities occurred during this study. No MOV-related clinical observations occurred during this study. There were no MOV-related changes in body weights.

To determine the potential mutagenicity of MOV by Pig-a mutation assay, blood samples were collected on Day 29 by abdominal aorta and were analyzed by flow cytometry. The negative and positive controls were within acceptance criteria. All the acceptance criteria were fulfilled, and therefore the test was concluded as valid.

No substantial reduction in the %RETs was observed for any of the MOV-treated groups (Groups 2, 3, and 4) when compared to the concurrent negative control (Group 1) value. Therefore, MOV did not cause cytotoxicity following daily oral administration up to 500 mg/kg/day for 28 consecutive days to male rats.

MOV treatment at doses up to 500 mg/kg/day resulted in a mutation rate in RBCs and reticulocytes similar to spontaneous background rates of untreated laboratory historical control animals [Figure 2.6.6: 1]. The mean RBC and RET mutation rates at the highest dose (500 mg/kg) were 2.6 and 10.98 mutations per million cells, respectively, each well within the historical control range (and 95% upper limit) for untreated control animals observed in the laboratory for RBC (0.4-7.78) and RET (0.57-16.08) and are thus considered to be not biologically meaningful. However, when compared to the concurrent negative control group, several MOV dose groups had statistically significant increases ($p \leq 0.05$) in mutant RBCs or RETs (RETs at 500 mg/kg/day and RBC at all dose levels). These increases relative to the concurrent control did not demonstrate a statistically significant dose-related trend when evaluated with an appropriate trend test and thus, 2/3 criteria for negative response and 1/3 criteria for positive response were met. According to the study protocol, all 3 criteria for positive or negative must be met, otherwise the assay results are categorized as ‘equivocal’, aligned with recommendations by the International Workshop on Genotoxicity Testing (IWGT) Workgroup for the in vivo Pig-a assay [Ref. 4.3: 05RB64].

Figure 2.6.6: 1 MOV In Vivo Mammalian Peripheral Blood Erythrocyte Pig-a Summary Results (TT #[redacted]-7808)



HC Historical control; PC positive control, Ethyl nitrosourea (ENU).

In conclusion, following the criteria for interpretation of results, MOV treatment resulted in equivocal results with regard to mutagenic effects to the RBCs and circulating RETs of male rats when administered up to 500 mg/kg/day for 28 consecutive days.

According to ICH S2 (R1) guideline on genotoxicity testing and data interpretation for pharmaceuticals intended for human use, “Examples of results that are not considered biologically meaningful include:

i. Small increases that are statistically significant compared with the negative or solvent control values but are within the confidence intervals of the appropriate historical control values for the testing facility

ii. Weak/equivocal responses that are not reproducible."

According to WHO/IPCS Harmonized Scheme on mutagenicity testing for chemical risk assessment [Ref. 4.3: 06FT2G], a second in vivo test is recommended as follow up to an equivocal in vivo mutagenicity result which should be "chosen on a case-by-case basis (ordinarily on a different end point or in a different tissue, depending on toxicokinetics, metabolism and mode of action); proceed according to 'positive' or 'negative'". The follow up in vivo assay chosen in this case was the Big Blue® Transgenic F344 Rat assay (*cII* locus). The Big Blue Assay is a Transgenic Rodent (TGR) mutation assay, described in OECD Test Guideline 488 (OECD, 2020). Mutation frequency was evaluated in a rapidly proliferating tissue, the bone marrow (the same tissue evaluated in the Pig-a Mutation Assay), and a slowly proliferating tissue, the liver.

4.2.3 In Vivo Mutation Assay at the c*II* Locus in Big Blue® Transgenic F344 Rats (TT #[redacted]-9025)

The purpose of this assay was to determine the effect of MOV on mutant frequency at the *cII* gene in liver and bone marrow following daily oral gavage administration to male transgenic Fischer 344 Big Blue® rats for 28 days [Sec. 2.6.7: 9C].

MOV was administered at the following dose levels: 0 (vehicle control), 50, 150 and 500 mg/kg/day (Groups 1-4, respectively), to six male Fischer 344 Big Blue® rats per group. 1% methylcellulose in deionized water was used as the vehicle. The dosing volume was 10 mL/kg. The high dose of 500 mg/kg/day was selected based on physical signs, including hunched posture and ruffled fur, and hematological changes observed in Fischer 344 rats orally administered MOV at 500 mg/kg/day for 7 days in a dose range-finding study (TT #[redacted]-9027) [Sec. 2.6.6: 8.7.3.1]. This dose was associated with NHC $AUC_{0\ 24hr}$ and C_{max} exposure higher than the human NHC $AUC_{0\ 24hr}$ and C_{max} exposure, based on toxicokinetic measurements from the range-finding study in male Fischer 344 rats [

Table 2.6.6: 43]. NHC and NHC-TP exposures in the rat bone marrow and liver were demonstrated in PK073 and PK067, respectively [Sec. 2.6.4].

Assessment of tolerability was based on mortality, clinical observations, body weights, and food consumption. Animals were sacrificed on Day 31. At necropsy, the liver (right medial lobe) and bone marrow were collected, flash frozen in liquid nitrogen and stored in a freezer set to -80°C. These tissues from the first five surviving animals/group were processed for DNA isolation and analysis of *cII* mutants, along with the DNA from the packaging positive controls.

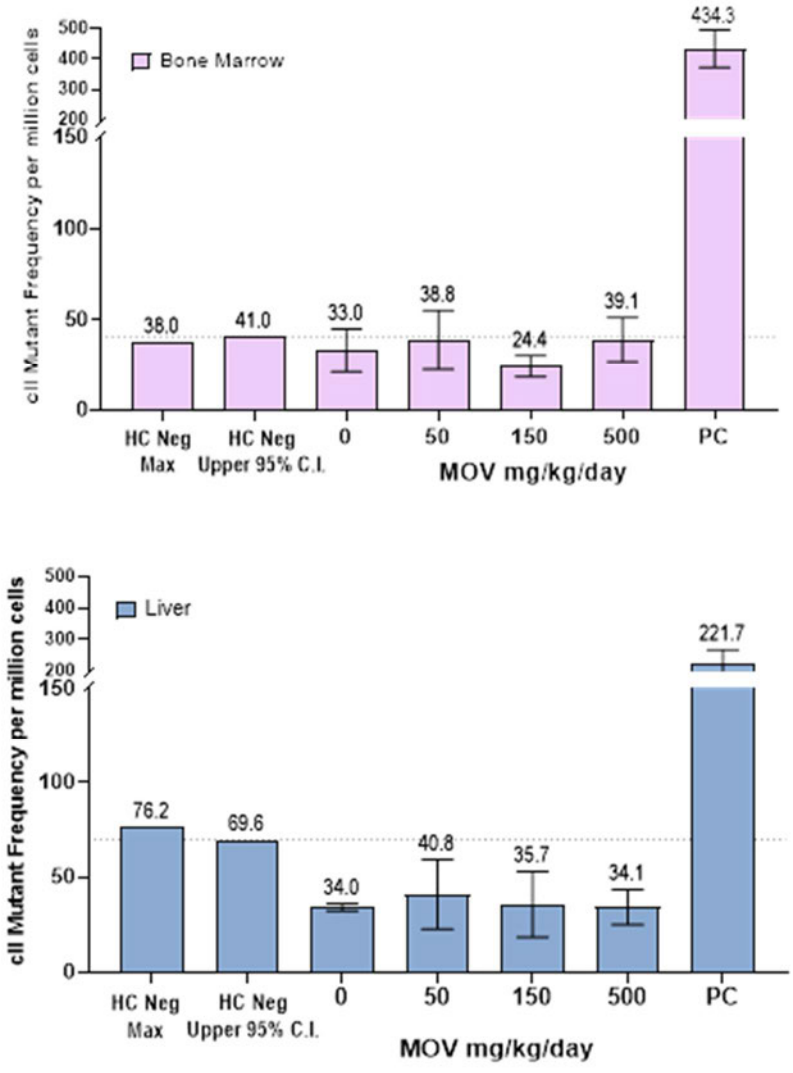
DNA isolated from previous study, positive control animals (F344 transgenic male rats exposed to N ethyl-N-nitrosourea (ENU) by oral gavage, at 20 mg/kg/day on 6 non-consecutive days) was used as a packaging positive control. ENU is a potent direct acting mutagen, demonstrated to be mutagenic in the target tissues.

There were no unscheduled deaths. Hunched posture was observed in 2 animals at 500 mg/kg/day. Compared to the vehicle control group, a decrease in mean body weight gain

was noted at 500 mg/kg/day (-21%), resulting in a decreased body weight (4.22%). There were no notable changes in food consumption.

Treatment with MOV in 1% methylcellulose in deionized water did not cause a statistically elevated mutant frequency at the c*II* gene in the liver or bone marrow of Big Blue® rats, when compared to controls. The ENU treatment produced a statistically significant increase in mutant frequencies for both tissues tested, demonstrating the utility of the test system to detect and quantify induced mutants, following exposure to a known direct acting mutagen [Figure 2.6.6: 2].

Figure 2.6.6: 2 MOV In Vivo Mutation Assay at the *cII* Locus in Big Blue® Transgenic F344 Rats Summary Results (TT #[redacted]-9025)



HC Historical control; PC positive control, Ethyl nitrosourea (ENU).

Under the conditions of this study, the administration of MOV at doses up to and including 500 mg/kg/day was negative for the induction of *cII* mutants in the liver and bone marrow of male transgenic Fischer 344 Big Blue® rats.

Transgenic and Pig-a rodent assays have demonstrated the capacity to sensitively detect in vivo mutagenic nucleoside analogs. Similar to MOV, an antiviral pyrimidine nucleoside analog, 5-(2-chloroethyl)-2 -deoxyuridine (CEDU) was positive in the Ames assay but negative in the in vitro and in vivo chromosomal damage assays [Ref. 4.3: 05R8C8] [Ref. 4.3: 05R7QV]. However, CEDU is a deoxynucleoside while MOV is a ribonucleoside and CEDU (unlike MOV) was clearly positive in a comparable transgenic rodent mutagenicity assay and Pig-a assay [Ref. 4.3: 05R8C8], [Ref. 4.3: 05R7QV]. CEDU was positive in the Mutamouse™ transgenic mutations assay [Ref. 4.3: 05R8C8] and showed robust dose-related increases in Pig-a mutant reticulocytes and mutant erythrocytes.

In conclusion, in two distinct rodent mutagenicity models, the impact of MOV treatment on mutation rates was not differentiable from background. A minimal equivocal increased mutant frequency relative to vehicle control in the peripheral blood erythrocyte Pig-a mutation assay (TT #[redacted]-7808) [Sec. 2.6.6: 4.2.2] was not reproduced in the Big Blue® Transgenic F344 rat assay (TT #[redacted]-9025). Consistent with ICH S2 (R1) (equivocal result which is not reproducible is overall negative) and based on the overall mutagenicity assessment conducted according to the criteria of the WHO IPCS scheme for mutagenicity testing [Ref. 4.3: 06FT2G], the overall result from the in vivo mutagenicity assessment demonstrated MOV was negative for genotoxicity in in vivo mammalian systems.

4.3 Other: Genotoxicity Data from Independent External Laboratory

An in vitro mutagenicity study was performed by an independent academic laboratory at the University of North Carolina demonstrating a concentration-dependent increase in rate of mutation in mammalian cells (CHO cells) at the hprt locus after 32 days of continuous in vitro exposure to NHC [Ref. :4.3: 07ZMDH]. The assay was conducted in extreme conditions as the duration of exposure (32 days) was significantly longer than the maximum 6 to 24 hours recommended in the OECD regulatory test guideline (OECD Test Guideline Test No. 476). Additionally, the absence of appropriate cytotoxicity assessments, the resulting lack of calculation of mutant frequency per surviving cell, the high variability in background mutation rate between cultures and likelihood of nucleoside pool imbalance due to accumulation of cytidine and uridine over the 32-day continuous exposure [Ref. 4.3: 07WZ24] make interpretation of the results and comparison with existing published HPRT assay data problematic. As such, the information on this nonstandard in vitro mutagenicity study does not meaningfully inform on human risk.

5 CARCINOGENICITY

No carcinogenicity studies have been completed.

6 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

6.1 Fertility and early embryonic development

6.1.1 A Fertility Study by Oral Gavage Administration in Female Rats (TT #[redacted]-9000)

The objective of this study was to test for potential effects on fertility in female rats resulting from once daily oral administration of MOV beginning approximately 2 weeks before cohabitation, and through mating and implantation. In addition, the TK profile of NHC was characterized [Sec. 2.6.7: 12A].

Female Crl:CD(SD) rats, approximately 13 weeks old at start of dose administration, were assigned to 4 groups of 30 females each (22/group for the main study and 8/group for the TK phase). Females were administered 100, 250, or 500 mg/kg/day of MOV in vehicle (1.0 % methylcellulose in deionized water) or vehicle only, once daily by oral gavage beginning 2 weeks prior to cohabitation, during cohabitation (up to 21 days) with untreated breeder males, and continuing until GD 7. The dosing volume was 10 mL/kg. The high dose was chosen based on unacceptable maternal toxicity observed at 1000 mg/kg/day in a previous pEFD toxicity study in rats (TT #[redacted]-7054) [Sec. 2.6.6: 6.2.1].

Assessment of general toxicity was based on mortality, clinical signs, body weights, food consumption, and macroscopic examination. Assessment of reproductive performance was based on estrous cyclicity (pre-dose and during the premating dosing phase), mating, fertility, and ovarian and uterine examinations on GD 13. Plasma NHC concentrations were determined in treated and control samples collected from rats in the TK phase on Study Day 15.

All MOV-treated animals survived until scheduled termination. There were no MOV-related clinical signs, macroscopic observations, or effects on mean female body weights or mean food consumption values in any group. There were no MOV-related effects on estrous cyclicity, mating, fertility, pregnancy indices, or early embryonic development.

The NHC TK parameters are presented in the following table [Table 2.6.6: 20].

Table 2.6.6: 20 Mean Plasma NHC TK Parameters in Female Rats Following Oral Dosing with MOV: Study Day 15 (TT #[redacted]-9000)

				Sex	
				Female	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
100	2	AUC_{0-24hr}	hr*µM	14.9	2.44
		C_{max}	µM	7.41	1.56
		T_{max}	hr	0.500	NC
250	3	AUC_{0-24hr}	hr*µM	61.4	9.72
		C_{max}	µM	31.5	4.57
		T_{max}	hr	1.00	NC
500	4	AUC_{0-24hr}	hr*µM	157	17.1
		C_{max}	µM	71.4	2.92
		T_{max}	hr	1.00	NC

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration.

NHC concentrations in plasma from all control group animals at 0.5 hour postdose were below the lower limit of quantitation of the bioanalytical method.

Following oral administration of MOV to female rats on Study Day 15, mean plasma NHC $AUC_{0\ 24hr}$ and C_{max} values were generally greater than dose proportional between 100 and 250 mg/kg/day, and were approximately dose proportional between 250 and 500 mg/kg/day.

In conclusion, there was no MOV-related maternal toxicity or effects on fertility and early embryonic development. Based on these results, the NOEL/NOAEL for general toxicity and female fertility parameters was ≥500 mg/kg/day ($AUC_{0\ 24hr}$ 157 µM *hr, 2.1-fold the clinical NHC exposure at 800 mg Q12H).

6.1.2 A Fertility Study by Oral Gavage Administration in Male Rats (TT #[redacted]-9012)

The objective of this study was to test for potential effects on fertility in male rats resulting from once daily oral administration of MOV beginning approximately two weeks before cohabitation, through mating, and until the day prior to sacrifice (approximately 6 weeks total). In addition, the TK profile of NHC was characterized [Sec. 2.6.7: 12B].

Male Crl:CD(SD) rats (approximately 11 weeks old at start of dose administration) were assigned to 4 groups of 30 males each (22 rats/group for the main study and 8 male rats/group for the TK phase). Males were administered 100, 250, or 500 mg/kg/day MOV in vehicle (1.0% methylcellulose in deionized water) or vehicle only once daily by oral gavage for 14 days before cohabitation, during cohabitation with untreated female rats, and continuing through Study Day 46. The dosing volume was 10 mL/kg. The high dose was chosen based on excessive decrements in weight gain and food consumption observed at

1000 mg/kg/day over the course of a 3-month oral toxicity study in rats (TT #[redacted]-1014) [Sec. 2.6.6: 3.2.3].

Assessment of general toxicity was based on mortality, clinical signs, body weights, food consumption, and macroscopic observations. Assessment of reproductive performance was based on mating, fertility, and ovarian and uterine examinations of the untreated female rats. Plasma NHC concentrations were determined in treated and control samples collected from rats in the TK phase on Study Day 15.

There were no MOV-related deaths, clinical signs, or macroscopic observations in male rats. At 500 mg/kg/day, mean male body weights, body weight gains, and food consumption values were reduced relative to respective mean control values. Mean body weight gain for the entire dose period was 21.3% below control. Mean food consumption values were reduced up to 11.5% below control. The pregnancy, mating, and fertility indices were comparable among the four dose groups. There were no MOV-related effects on early embryonic development.

The NHC TK parameters are presented in the following table [Table 2.6.6: 21].

Table 2.6.6: 21 Mean Plasma NHC TK Parameters in Male Rats Following Oral Dosing of MOV: Study Day 15 (TT #[redacted]-9012)

				Sex	
				Males	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
100	2	$AUC_{0\text{-}24hr}$	hr*µM	45.6	3.93
		C_{max}	µM	23.2	4.38
		T_{max}	hr	1.00	NC
250	3	$AUC_{0\text{-}24hr}$	hr*µM	179	12.7
		C_{max}	µM	64.6	7.77
		T_{max}	hr	1.00	NC
500	4	$AUC_{0\text{-}24hr}$	hr*µM	463	29.0
		C_{max}	µM	129	9.86
		T_{max}	hr	1.00	NC

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration.

NHC concentrations in plasma from all control group animals were below the lower limit of quantitation of the bioanalytical method.

Following oral administration of MOV at doses of 100, 250, and 500 mg/kg/day on Study Day 15, mean plasma NHC $AUC_{0\ 24hr}$ values were greater than dose proportional, and mean plasma NHC C_{max} values were approximately dose proportional across all doses.

In conclusion, MOV-related general toxicity was limited to the 500 mg/kg/day group and consisted of reductions in mean body weights, body weight gains, and food consumption relative to concurrent controls. These changes were nonadverse based on the magnitude of the effects and since they were not associated with evidence of impaired general condition of the animals. There were no MOV-related effects on fertility or early embryonic development. Based on these results, the NOEL was 250 mg/kg/day for general toxicity and ≥500 mg/kg/day for fertility parameters. The NOAEL for both general toxicity and fertility in males was ≥500 mg/kg/day ($AUC_{0\ 24hr}$ 463 µM*hr, 6.1-fold the clinical NHC exposure at 800 mg Q12H).

6.2 Embryo-fetal development

6.2.1 Preliminary Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rats (TT # [redacted]-7054)

The objectives of this GLP-compliant preliminary EFD study were to evaluate the potential for developmental toxicity of MOV in rats following oral administration from GD 6 through 17, and to evaluate the maternal TK profile of MOV and NHC on GD 15 [Sec. 2.6.7: 13A].

Mated female Crl:CD(SD) rats (GD 0 day of confirmed mating) were assigned to 5 groups of 16 presumed pregnant females each (with 8 per group assigned to the cesarean section component of the study; 8 per group assigned to TK evaluations). The animals were approximately 10 weeks of age at study start. From GD 6 through 17, females received 100, 200, 500, or 1000 mg/kg/day of MOV in vehicle (1.0% methylcellulose in deionized water) or vehicle only, once daily by oral gavage. The high dose was the limit dose for developmental and reproductive toxicity studies as per the ICH S5(R3) guideline. The dosing volume for all animals was 10 mL/kg.

Maternal toxicity was assessed based on mortality, clinical observations, body weights, food consumption, and gross examination limited to the thoracic and abdominal viscera. Plasma MOV and NHC concentrations were determined in samples collected on GD 15 from a subset of non-fasted rats in all groups. On GD 21, all surviving females were euthanized, gravid uterine weights were recorded, and the uterine contents of each female were examined. Evaluation of developmental toxicity was based on embryonic/fetal viability (as assessed by numbers of corpora lutea, implantations, and live fetuses per pregnant female), fetal weights and sex ratios, and fetal external, coronal, visceral, and skeletal morphology. Gross placental morphology was evaluated.

There was MOV-related mortality at 1000 mg/kg/day. Two females were euthanized on GD 10 due to excessive toxicity (body weight loss of 25.6 or 35.4 g [-11.7% or -15.7%] between GD 6 and 10). All remaining animals survived until scheduled termination.

In addition to body weight losses in the two females that led to early euthanasia on GD 10, there were transient MOV-related effects on average mean maternal body weight and body weight gain in females surviving to scheduled cesarean section at 1000 mg/kg/day. Mean maternal body weight gain in females assigned to the cesarean section component of the study were reduced at the beginning of the dose period (81% less than controls on GD 6 to

10) followed by gains that were comparable to controls for the remainder of the dose period and higher than controls following the dose period. Therefore, mean maternal body weight over the course of the study (GD 6 to 21) was comparable to controls. Associated with the early effects on maternal body weight, there were transient MOV-related reductions in mean maternal food consumption at 1000 mg/kg/day (25% less than controls for GD 6 to 8).

There were no MOV-related effects on body weight or food consumption at ≤500 mg/kg/day, and no MOV-related clinical signs occurred at any dose level tested.

There were no gross findings in the thoracic and abdominal viscera in any group.

At 1000 mg/kg/day, developmental toxicity included postimplantation losses, fetal malformations and variations, and reduced fetal growth. A MOV-related increase in postimplantation loss was observed in the 1000 mg/kg/day group (22.0%, versus 6.3% in controls). MOV-related malformations included abnormal and/or small eye/eye socket, absent kidney, rib malformations (primarily detached ribs), thoracic and lumbar vertebra malformations, and variations were limited to cervical ribs and trace supernumerary ribs. There were MOV-related reductions in mean live fetal body weights (23.5% and 26.4% less than controls in female and male fetuses, respectively) and associated delays in skeletal ossification (increased incidences of incomplete ossification of thoracic vertebrae and/or sternebrae and reduced mean number of ossified sacrocaudal vertebrae).

Developmental toxicity at 500 mg/kg/day was limited to decreased mean fetal body weights (6.7% and 10.8% relative to concurrent controls in female and male fetuses, respectively). While this finding was initially considered of uncertain relationship to treatment in this study, this finding repeated in the subsequent definitive EFD study in rats at 500 mg/kg/day (TT #[redacted]-7000) [Sec. 2.6.6: 6.2.2] and was consequently attributed to MOV treatment.

Slightly increased incidences of cervical ribs noted at 200 and 500 mg/kg/day and a rib malformation (detached rib) observed in one fetus at 200 mg/kg/day were initially considered of uncertain relationship to treatment. However, given that no MOV-related skeletal malformations or variations were observed in a subsequent definitive EFD study in rats at doses up to 500 mg/kg/day (TT #[redacted]-7000) [Sec. 2.6.6: 6.2.2], these findings were incidental and unrelated to MOV treatment.

The MOV and NHC TK parameters are presented in [Table 2.6.6: 22] and [Table 2.6.6: 23].

Table 2.6.6: 22 Mean Plasma MOV TK Parameters in Pregnant Rats Following Oral Dosing of MOV: Gestation Day 15 (TT #[redacted]-7054)

				Sex	
				Female	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
100	2	AUC_{0-24hr}	hr*µM	0.165	0.0399
		C_{max}	µM	0.116	0.0243
		T_{max}	hr	0.500	NC
200	3	AUC_{0-24hr}	hr*µM	0.272	0.0231
		C_{max}	µM	0.215	0.0358
		T_{max}	hr	0.500	NC
500	4	AUC_{0-24hr}	hr*µM	1.31	0.137
		C_{max}	µM	0.614	0.115
		T_{max}	hr	0.500	NC
1000	5	AUC_{0-24hr}	hr*µM	2.94	0.183
		C_{max}	µM	0.827	0.137
		T_{max}	hr	1.00	NC

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration.
a MOV concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation of the bioanalytical method.

Table 2.6.6: 23 Mean Plasma NHC TK Parameters in Pregnant Rats Following Oral Dosing of MOV: Gestation Day 15 (TT #[redacted]-7054)

				Sex	
				Female	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
100	2	AUC_{0-24hr}	hr*µM	22.5	1.56
		C_{max}	µM	12.1	2.47
		T_{max}	hr	0.500	NC
200	3	AUC_{0-24hr}	hr*µM	45.7	4.68
		C_{max}	µM	26.0	4.99
		T_{max}	hr	0.500	NC
500	4	AUC_{0-24hr}	hr*µM	217	25.3
		C_{max}	µM	103	16.3
		T_{max}	hr	1.00	NC
1000	5	AUC_{0-24hr}	hr*µM	570	62.2
		C_{max}	µM	207	48.4
		T_{max}	hr	1.00	NC

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration.
a NHC concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation of the bioanalytical method.

Mean plasma MOV and NHC $AUC_{0\ 24hr}$ values were approximately dose proportional between 100 and 200 mg/kg/day, and greater than dose proportional between 200 and 1000 mg/kg/day. Mean plasma MOV C_{max} values were approximately dose proportional between 100 and 500 mg/kg/day, and less than dose proportional between 500 and 1000 mg/kg/day. Mean plasma NHC C_{max} values were approximately dose proportional between 100 and 200 mg/kg/day, greater than dose proportional between 200 and 500 mg/kg/day, and approximately dose proportional between 500 and 1000 mg/kg/day.

In conclusion, maternal toxicity, including early sacrifice of 2 dams occurred at 1000 mg/kg/day (NHC $AUC_{0\ 24hr}$ 570 µM*hr, 7.5-fold the clinical NHC exposure at 800 mg Q12H). There was no maternal toxicity at 500 mg/kg/day (NHC $AUC_{0\ 24hr}$ 217 µM *hr, 2.9-fold the clinical NHC exposure at 800 mg Q12H). Developmental toxicity also occurred at 1000 mg/kg/day and included postimplantation losses, fetal malformations (eye/eye socket, kidney, axial skeleton), and variations (cervical ribs and trace supernumerary ribs), and reduced fetal growth (reductions in body weight and ossification). Developmental toxicity at 500 mg/kg/day was limited to a reduction in mean fetal body weights (6.7% and 10.8% in female and male fetuses, respectively). There was no developmental toxicity at ≤200 mg/kg/day ($AUC_{0\ 24hr}$ 45.7 µM*hr, 0.6-fold the clinical NHC exposure at 800 mg Q12H).

6.2.2 Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rats (TT #[redacted]-7000)

The objectives of this study were to evaluate the potential for developmental toxicity of MOV in rats following oral administration from GD 6 through 17 and to evaluate the maternal TK profile of NHC on GD 15 [Sec. 2.6.7: 13B].

Mated female Crl:CD(SD) rats (GD 0 day of confirmed mating) were assigned to 4 groups of 28 presumed pregnant females each (with 20 per group assigned to the cesarean section component of the study; 8 per group assigned to TK evaluations). The animals were approximately 10 weeks of age at study start. From GD 6 through 17, females received 100, 250, or 500 mg/kg/day of MOV in vehicle (1.0% methylcellulose in deionized water) or vehicle only, once daily by oral gavage. The high dose was chosen based on unacceptable maternal toxicity observed at dose levels 1000 mg/kg/day in a previous preliminary embryo-fetal developmental toxicity study in rats. The dosing volume for all animals was 10 mL/kg.

Assessment of maternal toxicity was based on mortality, clinical observations, body weights, food consumption, and gross examination limited to the thoracic and abdominal viscera. Plasma NHC concentrations were determined in samples collected on GD 15 from a subset of non-fasted rats in all groups. On GD 21, all surviving females were euthanized, gravid uterine weights were recorded, and the uterine contents of each female were examined. Evaluation of developmental toxicity was based on embryonic/fetal viability (as assessed by numbers of corpora lutea, implantations, and live fetuses per pregnant female), fetal weights and sex ratios, and fetal external, coronal, visceral, and skeletal morphology. Gross placental morphology was evaluated.

All females survived to scheduled termination. At 500 mg/kg/day, there was a MOV-related reduction in mean maternal body weight gain from GD 6 to 8 (40% less than controls), resulting in a slight reduction in the overall mean gain for the dose period (8.4% less than controls from GD 6 to 18). An associated MOV-related reduction in mean maternal food consumption also occurred from GD 6 to 8 at 500 mg/kg/day (13% less than controls). There were no MOV-related effects on maternal body weight or food consumption at ≤250 mg/kg/day, and no clinical observations occurred in any group.

MOV-related fetal growth delay occurred at 500 mg/kg/day, as evidenced by reductions in mean live fetal body weights (11% and 13% less than controls in females and males, respectively) and reduced mean number of ossified sacrocaudal vertebrae (10.0 versus 10.9 in controls). Fetal growth was comparable to controls at ≤250 mg/kg/day, and there were no MOV-related effects on embryonic/fetal viability, fetal sex ratios, or fetal external, coronal, visceral, and skeletal morphology at any dose tested. There were no MOV-related placental abnormalities.

The mean NHC TK parameters are presented in [Table 2.6.6: 24]. Based on minimal plasma exposure to MOV observed in the pEFD rat study (TT #[redacted]-7054) [Sec. 2.6.6: 6.2.1], TK analysis was limited to NHC in this study (TT #[redacted]-7000).

Table 2.6.6: 24 Mean Plasma NHC TK Parameters in Pregnant Female Rats Following Oral Dosing of MOV: Gestation Day 15 (TT #[redacted]-7000)

				Sex	
				Female	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
100	2	$AUC_{0\text{-}24hr}$	hr*µM	18.4	2.00
		C_{max}	µM	11.4	1.57
		T_{max}	hr	1.00	NC
250	3	$AUC_{0\text{-}24hr}$	hr*µM	58.3	7.99
		C_{max}	µM	34.2	7.02
		T_{max}	hr	1.00	NC
500	4	$AUC_{0\text{-}24hr}$	hr*µM	NC	NC
		C_{max}	µM	NC	NC
		T_{max}	hr	NC	NC

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration.
NHC concentrations in plasma samples from all control group animals were below the lower limit of quantitation of the bioanalytical method.

Following repeated daily oral doses of MOV to pregnant female rats, mean plasma NHC $AUC_{0\ 24hr}$ and C_{max} values were generally dose-proportional between 100 and 250 mg/kg/day. Due to inaccurate plasma sample volumes collected 0.5, 1, 2 and 4 hours postdose at 500 mg/kg/day, no $AUC_{0\ 24\ hr}$, C_{max}, or T_{max} values could be calculated for that dose group. In the previous GLP pEFD study in rats (TT #[redacted]-7054), the mean plasma NHC $AUC_{0\ 24hr}$, C_{max}, and T_{max} values following repeated daily oral doses of MOV to pregnant female rats at 500 mg/kg/day were 217 hr*µM, 103 µM, and 1.00 hr, respectively.

In conclusion, maternal toxicity, including overall decreased body weight gain and transient decreased food consumption was noted at 500 mg/kg/day (NHC $AUC_{0\ 24hr}$ 217 µM*hr, 2.9-fold the clinical NHC exposure at 800 mg Q12H). Developmental toxicity also occurred at 500 mg/kg/day and was limited to reduced fetal growth (reductions in fetal body weight and numbers of ossified sacrocaudal vertebrae). Based on these results, the NOEL/NOAEL for both maternal and developmental toxicity was 250 mg/kg/day (NHC $AUC_{0\ 24hr}$ 58.3 µM*hr, 0.8-fold the clinical NHC exposure at 800 mg Q12H).

6.2.3 Preliminary Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rabbits (TT #[redacted]-7064)

The objectives of this GLP-compliant preliminary EFD study were to evaluate the potential for developmental toxicity of MOV in rabbits following oral administration from GD 7 through 19 and to evaluate the maternal TK profile of MOV and NHC on GD 15 [Sec. 2.6.7: 13C].

Mated female Dutch Belted rabbits (GD 0 day of confirmed breeding) were assigned to 5 groups of 12 presumed pregnant females each (with 8 per group assigned to the cesarean section component of the study; 4 per group assigned to TK evaluations). The animals were approximately 25 to 30 weeks of age at study start. From GD 7 through 19, females received 60, 200, 500, or 1000 mg/kg/day of MOV in the vehicle (1% [w/v] methylcellulose in deionized water) or vehicle only, once daily by oral gavage. The high dose was the limit dose for developmental and reproductive toxicity studies as per ICH S5(R3) guideline. The dosing volume for all animals was 5 mL/kg.

Assessment of maternal toxicity was based on mortality, clinical observations, body weights, food consumption, and gross examination limited to the thoracic and abdominal viscera. Plasma MOV concentrations were determined from samples collected on GD 15. On GD 28, all remaining females were euthanized, gravid uterine weights were recorded, and the uterine contents of each female were examined. Evaluation of developmental toxicity was based on embryonic/fetal viability (as assessed by numbers of corpora lutea, implantations, and live fetuses per pregnant female), fetal weights and sex ratios, and fetal external, coronal, visceral, and skeletal morphology. Gross placental morphology was also evaluated.

All females survived to scheduled termination.

At 1000 mg/kg/day, there were MOV-related clinical observations and effects on mean maternal body weight, body weight gain, and food consumption during the dosing period. Decreased fecal output was observed in 2/12 animals for one to six days. Mean maternal food

consumption was reduced from GD 7 to 8, GD 12 to 13 and GD 16 to 17 (14%, 37%, and 29% less than controls, respectively). Mean maternal body weight gain in females assigned to the cesarean section component of the study was reduced from GD 7 through 20 (41% less than controls). Furthermore, there was body weight loss (8% to 9%) in one female assigned to the cesarean section component and two females assigned to the TK component of the study. There were no MOV-related clinical observations or effects on maternal body weight or food consumption at 60, 200, or 500 mg/kg/day and no MOV-related gross findings in the thoracic and abdominal viscera in any group.

There were no MOV-related effects on embryonic/fetal survival, fetal sex ratios, live fetal weights, or fetal external, visceral, coronal, or skeletal morphology in any group. There were no placental abnormalities observed in any group.

The mean MOV TK parameters are presented in [Table 2.6.6: 25].

Table 2.6.6: 25 Mean Plasma MOV TK Parameters in Pregnant Female Rabbits Following Oral Dosing of MOV: Gestation Day 15 (TT #[redacted]-7064)

				Sex	
				Female	
Dose (mg/kg/day)[a,b]	Group	Parameter	Units	Mean	SE
60	2	AUC_{0-24hr}	hr*µM	0.276	0.0685
		C_{max}	µM	0.0444	0.0187
		T_{max}	hr	2.63	0.851
500	4	AUC_{0-24hr}	hr*µM	0.506	0.0213
		C_{max}	µM	0.139	0.0111
		T_{max}	hr	0.625	0.125
1000	5	AUC_{0-24hr}	hr*µM	0.702	0.0398
		C_{max}	µM	0.205	0.0391
		T_{max}	hr	0.667	0.167

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; SE standard error; T_{max} time of maximum concentration.

a MOV was detected in plasma from control rabbit #[redacted] 0003 at 7 hours following dosing on Gestation Day 15. Given the low MOV concentration detected, low incidence, and lack of concurrent NHC detection, it was confirmed that the animal was not dosed with MOV.

b Data for the 200 mg/kg/day group (group 3) were not reported due to incorrect plasma sample volumes collected that impacted MOV results.

Mean plasma MOV $AUC_{0\ 24hr}$ and C_{max} values were generally less than dose proportional between 60 and 1000 mg/kg/day. Toxicokinetic data for NHC were not reported because of lack of reproducibility of the bioanalytical data (incurred sample reproducibility failure) for

this analyte. However, NHC TK parameters in pregnant rabbits are provided for the EFD study in rabbits at doses of 125, 400, and 750 mg/kg/day (TT #[redacted]-7010) [Sec. 2.6.6: 6.2.4].

In conclusion, MOV-related maternal toxicity occurred at 1000 mg/kg/day and consisted of decreased fecal output, reduced maternal body weight gain, and reduced food consumption. No MOV-related maternal toxicity was observed at doses ≤500 mg/kg/day, and no MOV-related developmental toxicity was observed at any dose level.

6.2.4 Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rabbits (TT #[redacted]-7010)

The objectives of this study were to evaluate the potential for developmental toxicity of MOV in rabbits following oral administration from GD 7 through 19 and to evaluate the maternal TK profile of NHC on GD 15 [Sec. 2.6.7: 13D].

Mated female Dutch Belted rabbits (GD 0 day of confirmed breeding) were assigned to 4 groups of 23 presumed pregnant females each (with 19 per group assigned to the cesarean section component of the study; 4 per group assigned to TK evaluations). The animals were approximately 28 to 29 weeks of age at study start. From GD 7 through 19, females received 125, 400, or 750 mg/kg/day of MOV in the vehicle (1% [w/v] methylcellulose in deionized water) or vehicle only, once daily by oral gavage. The high dose was chosen based on unacceptable maternal toxicity observed at 1000 mg/kg/day in a previous preliminary oral embryo-fetal developmental toxicity study in rabbits. The dosing volume for all animals was 5 mL/kg.

Assessment of maternal toxicity was based on mortality, clinical observations, body weights, food consumption, and gross examination limited to the thoracic and abdominal viscera. Plasma NHC concentrations were determined from samples collected on GD 15. On GD 28, all remaining females were euthanized, gravid uterine weights were recorded, and the uterine contents of each female were examined. Evaluation of developmental toxicity was based on embryonic/fetal viability (as assessed by numbers of corpora lutea, implantations, and live fetuses per pregnant female), fetal weights and sex ratios, and fetal external, coronal, visceral, and skeletal morphology. Gross placental morphology was also evaluated.

All females survived to scheduled termination. At ≥400 mg/kg/day, mean maternal food consumption was reduced during the dosing period (maximal reductions of 27% and 42% at 400 and 750 mg/kg/day, respectively, from GD 12 to 13), and increased incidences of abnormal fecal output (no, scant, and/or unformed feces) were observed. Associated with the decreased mean maternal food consumption, there were MOV-related effects on mean maternal body weight gain. Mean maternal body weight gain in females assigned to the cesarean section component of the study was reduced from GD 7 to 20 (30% and 18% less than controls at 400 and 750 mg/kg/day, respectively) and remained reduced after completion of dosing (13% and 18% less than controls at 400 and 750 mg/kg/day from GD 20 to 28, respectively). No MOV-related gross findings were observed in the thoracic and abdominal viscera in any group.

There were no MOV-related effects on embryonic/fetal survival, fetal sex ratios, or fetal external, visceral, coronal, or skeletal morphology in any group. There were MOV-related reductions in mean live fetal body weights at 750 mg/kg/day (8.5% and 10% less than controls in female and male fetuses, respectively). No MOV-related effects on mean live fetal weights were observed at ≤400 mg/kg/day, and there were no placental abnormalities observed in any group.

The NHC TK parameters are presented in [Table 2.6.6: 26]. Based on minimal plasma exposure to MOV observed in the pEFD rabbit study (TT #[redacted]-7064) [Sec. 2.6.6: 6.2.3], TK analysis was limited to NHC in this study (TT #[redacted]-7010).

Table 2.6.6: 26 Mean Plasma NHC TK Parameters in Rabbits Following Oral Dosing of MOV: Gestation Day 15 (TT #[redacted]-7010)

				Sex	
				Female	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
125	2	$AUC_{0\text{-}24hr}$	hr*µM	111	9.04
		C_{max}	µM	65.4	4.69
		T_{max}	hr	0.750	0.144
400	3	$AUC_{0\text{-}24hr}$	hr*µM	490	33.3
		C_{max}	µM	204	22.3
		T_{max}	hr	1.00	0.00
750	4	$AUC_{0\text{-}24hr}$	hr*µM	1,360	113
		C_{max}	µM	379	23.2
		T_{max}	hr	1.13	0.315

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; SE standard error; T_{max} time of maximum concentration.
NHC concentrations in plasma from all control group animals were below the lower limit of quantitation of the bioanalytical method.

Following oral dosing of MOV to pregnant female rabbits, mean plasma NHC $AUC_{0\ 24hr}$ values were slightly greater than dose proportional and mean plasma NHC C_{max} values were generally dose proportional between MOV doses of 125 and 750 mg/kg/day.

In conclusion, MOV-related maternal toxicity occurred at ≥400 mg/kg/day and consisted of reduced mean food consumption and mean body weight gain, and abnormal fecal output. Developmental toxicity occurred at 750 mg/kg/day (NHC $AUC_{0\ 24hr}$ 1360 µM*hr, 18-fold the clinical NHC exposure at 800 mg Q12H) and was limited to reduced mean fetal body weights. Based on these results, the NOELs/NOAELs for maternal and developmental toxicity were 125 mg/kg/day (NHC $AUC_{0\ 24hr}$ 111 µM*hr, 1.5-fold the clinical NHC exposure at 800 mg Q12H) and 400 mg/kg/day (NHC $AUC_{0\ 24hr}$ 490 µM*hr, 6.5-fold the clinical NHC exposure at 800 mg Q12H), respectively.

6.3 Prenatal and postnatal development, including maternal function

6.3.1 A Pre- and Postnatal Development Study by Oral (Gavage) in Rats, Including a Postnatal Behavioral/Functional Evaluation (TT #[redacted]-9010)

The objectives of this study were to detect potential effects of MOV on Sprague Dawley CD (Crl:CD[SD]) female rats and development of the offspring, when administered orally from implantation through lactation and weaning [Sec. 2.6.7: 14]. Observations were continued through sexual maturity of the F1 generation offspring. In addition, the TK characteristics of MOV and NHC were determined from a limited number of F0 females on LD 10/11 and from F1 pups on PND 10.

Female Crl:CD(SD) rats (59 to 76 days old at start of dose administration) were assigned to 4 groups of 30 females each (22/group for the main study and 8/group for the TK phase). Females were administered 100, 250, or 500 mg/kg/day of MOV in vehicle (1.0% methylcellulose in deionized water) or vehicle only once daily by oral gavage beginning on GD 6 and continuing through LD 20. The dosing volume was 10 mL/kg. The high dose was chosen based on unacceptable maternal toxicity observed at 1000 mg/kg/day in a previous preliminary oral embryo-fetal developmental toxicity study in rats with MOV (TT #[redacted]-7054) [Sec. 2.6.6: 6.2.1].

Assessment of general toxicity was based on mortality, clinical signs, body weights, food consumption, parturition, lactation, and maternal behavior. F0 generation females were allowed to deliver naturally and were monitored to weaning (LD 21), at which time F1 generation offspring (1/sex/litter) were selected for continuation on study.

Assessment of preweaning F1 development was based on viability, clinical signs, body weight, and developmental landmarks. Assessment of postweaning F1 development was based on viability, clinical signs, body weights, food consumption, sexual maturation, changes in behavior (as evaluated by motor activity, acoustic startle habituation, and Morris water maze), reproductive performance, fertility, and macroscopic necropsy observations.

There were no MOV-related deaths in the F0 generation females or F1 generation male and female rats.

There were no MOV-related maternal (F0) clinical signs or macroscopic necropsy observations. Mean maternal body weight gains were statistically significantly decreased in the 250 and 500 mg/kg/day dose groups from GD 6 to 20 (10% and 13% below control, respectively) primarily due to transient decrements in mean body weight gains from GD 15 to 18 in the 250 mg/kg/day group and from GD 15 to 20 in the 500 mg/kg/day group. At both doses, the decreased body weight gains did not persist during the lactation phase and were non-adverse. There were no MOV-related effects on maternal (F0) food consumption during the gestation and lactation phase or any natural delivery parameter in the F0 females.

There were no MOV-related effects on the F1 pup clinical condition or body weight during the preweaning phase and no MOV-related clinical signs, necropsy observations or effects on

body weight, food consumption, developmental landmarks, sexual maturation, behavioral endpoints, or reproductive endpoints in the F1 rats during the postweaning phase.

Mean values of the LD 10 TK parameters are presented in [Table 2.6.6: 27] and [Table 2.6.6: 28].

Table 2.6.6: 27 Mean Maternal Plasma MOV TK Parameters in Rats Following Oral Dosing of MOV: Lactation Day 10 (TT #[redacted]-9010)

				Sex	
				Female	
Dose (mg/kg/day)	**Group**	**Parameter**	**Units**	**Mean**	**SE**
100	2	$AUC_{0\text{-}24hr}$	hr*µM	0.190	0.0282
		C_{max}	µM	0.155	0.0156
		T_{max}	hr	0.500	NC
250	3	$AUC_{0\text{-}24hr}$	hr*µM	0.786	0.168
		C_{max}	µM	0.569	0.113
		T_{max}	hr	0.500	NC
500	4	$AUC_{0\text{-}24hr}$	hr*µM	1.79	0.176
		C_{max}	µM	0.953	0.145
		T_{max}	hr	0.500	NC

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration

MOV concentrations in plasma from all control group animals at 0.5 hours postdose were below the lower limit of quantitation of the bioanalytical method.

Table 2.6.6: 28 Mean Maternal Plasma NHC TK Parameters in Rats Following Oral Dosing of MOV: Lactation Day 10 (TT #[redacted]-9010)

				Sex	
				Female	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE
100	2	$AUC_{0\text{-}24hr}$	hr*µM	9.12	1.70
		C_{max}	µM	7.67	2.92
		T_{max}	hr	0.500	NC
250	3	$AUC_{0\text{-}24hr}$	hr*µM	62.6	7.26
		C_{max}	µM	34.0	4.62
		T_{max}	hr	1.00	NC
500	4	$AUC_{0\text{-}24hr}$	hr*µM	122	16.7
		C_{max}	µM	75.3	20.5
		T_{max}	hr	1.00	NC

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration
NHC concentrations in plasma from all control group animals at 0.5 hours postdose were below the lower limit of quantitation of the bioanalytical method.

Mean plasma MOV and NHC $AUC_{0\ 24hr}$ and C_{max} values were greater than dose proportional between 100 and 250 mg/kg/day, and dose proportional between 250 mg/kg/day and 500 mg/kg/day; except for mean MOV C_{max} values that were approximately dose proportional across all doses.

No MOV was detected in plasma from PND 10 pups at 0.5 and 1 hour postdose; NHC was detected in pups with concentrations less than 0.09% of mean plasma concentrations achieved in maternal rats at respective times.

Based on the non-adverse transient decreased mean body weight gain during pregnancy at ≥250 mg/kg/day, the general toxicity NOEL for MOV in the F0 dams was 100 mg/kg/day and the NOAEL was ≥500 mg/kg/day ($AUC_{0\ 24hr}$ 122 µM*hr, 1.6-fold the clinical NHC exposure at 800 mg Q12H). The developmental NOEL/NOAEL for viability and growth in the F1 offspring was ≥500 mg/kg/day. There were no MOV-related effects on growth, sexual maturation, or neurobehavioral or reproductive function in the F1 generation rats at any dose.

6.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Studies in juvenile animals have not been completed.

7 LOCAL TOLERANCE

Local tolerance was assessed as part of the repeat-dose toxicity studies in mice, rats and dogs [Sec. 2.6.6: 3]. There was no evidence of a local effect of MOV on the gastrointestinal tract

in the GLP repeat dose toxicity studies in mice, rats or dogs. The focal hemorrhages observed in the gastrointestinal tract in the 28-day dog study were attributable to severe thrombocytopenia.

In addition, two local tolerance studies (a bovine corneal opacity and permeability test [Sec. 2.6.6: 7.1] and a MatTek EpiDerm™ MTT viability assay [Sec. 2.6.6: 7.2]), were conducted in support of the occupational safety program.

7.1 Bovine Corneal Opacity and Permeability Test (BCOP) (TT #[redacted]-7801)

The objective of this study was to determine the potential for ocular irritation using an alternative to the Draize methodology [Sec. 2.6.7: 16]. Five corneas were dosed with 0.75 g of neat MOV. Opacity measurements and sodium fluorescein permeability were determined. MOV was classified as a mild irritant in this assay.

7.2 MatTek EpiDerm™ MTT Viability Assay (TT #[redacted]-7802)

The objective of this study was to provide an estimate of dermal irritation potential using an alternative to the Draize methodology [Sec. 2.6.7: 16]. The MatTek EpiDerm™ MTT Viability Assay has been demonstrated to be a quantitative method for assessing potential skin hazards.

MatTek EpiDerm™ tissue samples were treated in duplicate with MOV (100 mg) for 1, 4 and 24 hours or with 0.1% Triton® X-100 (positive control) for 4 and 9 hours. A negative control (undosed tissue) was tested in the same manner for 4 hours only. Following treatment, the viability of the tissues was determined using thiazole blue tetrazolium bromide (MTT) uptake and reduction. The absorbance of each sample was measured at 540 nm using a reference wavelength of 690 nm. The viability was then expressed as a percent of negative control values. The mean percent viability for each time point was used to calculate an ET_{50}, which represents the time at which the EpiDerm™ tissue viability was reduced 50% compared to control tissues. The ET_{50} scores were converted to an irritancy classification.

MOV was classified as a very mild irritant in this assay (ET_{50} score of 13.7 hr compared to 5.7 hr for the positive control).

8 OTHER TOXICITY STUDIES

8.1 Antigenicity/Immunogenicity

There were no observations or changes considered to be due to potential antigenicity induced by the test article in the repeat-dose toxicity studies [Sec. 2.6.6: 3]. Therefore, no antigenicity / immunogenicity evaluations were conducted.

8.2 Immunotoxicity

MOV is not associated with a cause for immunotoxicity concern and no additional immunotoxicity study was conducted. The hematopoietic/bone marrow toxicity and

associated hematological findings observed in dogs at NHC AUC exposure lower than the clinical NHC AUC exposure affected all blood progenitor cell lines, including immune system progenitor cells. According to ICH S8 guideline, specific assays to determine immunotoxicity for such compounds are not valuable in drug risk assessment. It is also important to note that similar findings were not observed in rats exposed to 15-fold the clinical NHC AUC exposure for 3 months, in mice exposed to 19-fold the clinical NHC AUC exposure for 1 month, in nonhuman primates exposed to 4-fold the clinical NHC AUC exposure for 1 week, and in rabbits exposed to 29-fold the clinical NHC AUC exposure for 2 weeks, and that there were no hematologic changes indicative of bone marrow toxicity or immunosuppression in clinical trials.

With the exception of the bone marrow toxicity in dogs only, there were no direct MOV-related alterations in immune system organ weights and/or histology (e.g., changes in thymus, spleen, lymph nodes). The decreased spleen and thymus weights, and the decreased cellularity of the lymphoid tissue of the spleen, thymus and lymph node observed at 1000 mg/kg/day in male rats 3-month rat study were secondary to stress [Ref. 4.3: 07XDNW] associated with notable decreased body weight gain noted at this dose (-55% compared to controls).

There were no changes in serum globulins in any nonclinical species. There were no infections or tumors observed in the repeat-dose toxicity studies.

In conclusion, aside from the well-characterized monitorable and reversible hematopoietic/bone marrow toxicity and associated hematologic findings observed in dogs, there was no indication of immunotoxicity observed in the repeat-dose toxicity studies. As such, in accordance with ICH S8 Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals, no additional immunotoxicity studies are warranted.

In support of the occupational safety program, a local lymph node assay (LLNA) in mice was conducted and is presented below in [Sec. 2.6.6: 8.2.1].

8.2.1 Local Lymph Node Assay in Mice (LLNA) (TT #[redacted]-7803)

In a local lymph node assay conducted in mice, MOV [25% (w/v) in N,N-Dimethylformamide (DMF)], a positive control (25% v/v hexylcinnamaldehyde), or vehicle control (DMF) were administered by topical application to the dorsum of each ear of 5 female CBA/J mice once daily for three consecutive days [Sec. 2.6.7: 17A].

At sacrifice, the auricular lymph nodes were isolated, single-cell suspensions of lymph node cells (LNC) were generated, and the LNC suspensions were analyzed by flow cytometry for 5-bromo-2'-deoxyuridine (BrdU) incorporation. The amount of proliferating (BrdU+) LNC was determined as a measure of the proliferative response of the local lymph node.

The 25% test article formulation induced no dermal reactions (erythema). On average, ear thickness remained the same (0.0% change) from experimental start to termination. The sensitivity index (SI) following the 25% test article treatment was 3.2. MOV was considered a dermal sensitizer in this assay.

8.3 Mechanistic

The mechanism of action of MOV efficacy was assessed as part of the primary pharmacodynamics studies. No additional mechanistic studies were conducted.

8.4 Dependence

There was no indication that MOV/NHC has a pharmacologic profile (including off-target profile) consistent with drug abuse liability potential. In addition, NHC-TP levels were shown to be lower in the brain compared to other tissues (i.e. lung and spleen) in the tissue distribution studies in rats, dogs, monkeys and ferrets [Sec. 2.6.4] and there was no evidence of psychoactive effects (i.e., sedative or stimulant effects) in the safety pharmacology or routine repeat-dose toxicity studies. As such, no abuse potential studies were conducted in animals.

8.5 Metabolites

Based on in vitro and in vivo nonclinical metabolism data detailed below, there is no expectation of human circulating metabolites other than the well-characterized NHC and endogenous pyrimidines and/or pyrimidine anabolites/catabolites, and therefore no metabolite toxicity studies were warranted.

In vitro in rat, dog and human hepatocytes, [^{14}C]MOV is rapidly hydrolyzed to [^{14}C]NHC, which is then metabolized to [^{14}C]cytidine and/or [^{14}C]uridine with further anabolism and catabolism of these endogenous nucleosides [Sec. 2.6.4]. Based on metabolism studies in rats and dogs with [^{14}C]MOV, the only metabolites identified in plasma were [^{14}C]NHC and [^{14}C]cytidine, [^{14}C]uridine and their anabolites/catabolites. A human ADME study with labeled MOV is not planned given the majority of the [^{14}C]MOV dose in animals appeared to be converted to endogenous [^{14}C]pyrimidine anabolites/catabolites and therefore were retained in the body.

8.6 Impurities

MOV impurities and degradation products were qualified according to ICH Q3A(R2) and ICH Q3B(R2) guidelines. NHC (proposed specification: [redacted]%) is a significant metabolite of MOV in rats, dogs, and humans, and is therefore qualified per ICH Q3A(R2) and ICH Q3B(R2) guidelines. The animal/human dose multiple for the [redacted] (also known as [redacted]), qualified by virtue of its presence in the batch evaluated in the 28-day oral toxicity study in rats with a 14-day recovery period (TT #[redacted]-7814), is presented in [Table 2.6.6: 29]. The Maximum Qualified Level parameter was calculated for the daily clinical dose of 1600 mg (800 mg Q12Hr).

Table 2.6.6: 29 Impurity and Dose Multiples

Impurity	Toxicology Study Content % impurity	NOAEL[a]	Maximum Qualified Level[b,c]
[redacted]	[redacted][d]	500 mg/kg/day	[redacted]%

a NOAEL (No Observe Adverse Effect Level) from the Oral 28 Day Toxicology and Toxicokinetics Study in Rats with a 14 Day Recovery (TT# [redacted] 7814) using API batch [redacted].

b Based on a clinical dose of 1600 mg [800 mg B.I.D.].

c Qualified level [% impurity x non clinical dose (mg/kg/day)] / [body surface area conversion factor (i.e., 5 for rats) x maximum clinical dose (i.e., 32 mg/kg/day for 50 kg body weight and 1600 mg clinical dose)].

d [redacted].

In addition, potential and actual impurities, including identified impurities in each starting material, intermediate, and drug substance/product, have been assessed for mutagenic potential according to ICH M7(R1) guideline, as described in Quality documents [Sec. 3.2.S.3.2] (Drug Substance) and [Sec. 3.2.P.5.5] (Drug Product).

8.7 Other

8.7.1 Photoreactivity Assessment of MOV and NHC (TT #[redacted]-7814)

MOV and NHC absorb light between 290 and 700 nm with a MEC > 1000 $M^{1}cm^{1}$ [Sec. 2.6.7: 17B]. However, neither MOV or NHC were shown to not generate ROS, including superoxide anion and singlet oxygen at an aqueous concentration of 200 µM, and were not photoreactive. As such, MOV and NHC have low probability of being phototoxic in humans, and further phototoxicity testing is not warranted per ICH S10, Photosafety Evaluation of Pharmaceuticals guideline.

8.7.2 Toxicokinetic Studies

8.7.2.1 A 7-Day Oral Gavage Toxicokinetic Study in Wild Type CByB6F1 Tg(HRAS)2Jic Mice (TT #[redacted]-9011)

The purpose of this study was to determine the TK profile of NHC following daily oral (gavage) administration with MOV to rasH2 WT mice (hybrid) for 7 days [Sec. 2.6.7: 17C]. RasH2 WT mice (hybrid) were assigned to 4 groups of 18 females and 18 males each receiving 100, 300, 700, or 2000 mg/kg of MOV in 1% methylcellulose in deionized water. The dosing volume for was 10 mL/kg.

Assessment of tolerability was based on mortality, clinical observations, body weights, and food consumption. Plasma NHC concentrations in treated animals were determined on Study Day 7.

There was no mortality during the study. There were no clinical signs noted during the study in any treatment groups, and body weights and food consumption were comparable between groups.

Mean plasm NHC TK parameters are presented in [Table 2.6.6: 30].

Table 2.6.6: 30 Mean Plasma NHC TK Parameters in Mice Following Oral Dosing of MOV: Study Day 7 (TT #[redacted]-9011)

				Sex					
				Female		Male		Sex-Combined	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE	Mean	SE
100	1	$AUC_{0\text{-}24hr}$	hr*µM	24.8	1.67	34.4	4.49	29.6	2.68
		C_{max}	µM	22.8	0.747	24.7	1.95	23.8	1.03
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
300	2	$AUC_{0\text{-}24hr}$	hr*µM	71.0	3.24	82.5	4.44	76.8	3.25
		C_{max}	µM	78.1	5.53	71.8	6.59	74.9	4.10
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
700	3	$AUC_{0\text{-}24hr}$	hr*µM	199	13.1	272	17.6	236	13.4
		C_{max}	µM	205	19.9	223	22.1	214	13.9
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC
2000	4	$AUC_{0\text{-}24hr}$	hr*µM	1,190	130	1,640	74.9	1,420	86.1
		C_{max}	µM	844	120	1,080	122	960	92.5
		T_{max}	hr	0.500	NC	0.500	NC	0.500	NC

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration.

Following daily oral dosing of MOV, no substantial sex differences in plasma NHC $AUC_{0\ 24hr}$ and C_{max} values were observed on Study Day 7. Mean plasma NHC $AUC_{0\ 24hr}$ and C_{max} values were approximately dose proportional between 100 and 700 mg/kg/day MOV doses, and greater than dose proportional between 700 and 2000 mg/kg/day.

8.7.2.2 Exploratory 5-Day Oral Toxicokinetic Study in Sprague Dawley and Fischer 344 Rats (TT #[redacted]-1015)

The purpose of this study was to determine the TK profile of MOV and NHC when MOV was administered orally to male Sprague Dawley and Fischer 344 rats for 5 days [Sec. 2.6.7: 17C].

Male Crl:CD(SD) rats and male Fischer 344 WT:F344/NHsd rats (3 groups of each strain; 11 males/group) received 50, 150, or 500 mg/kg/day of MOV in 1.0% (w/v) methylcellulose in deionized water, at a dose volume of 10 mL/kg. Daily observations for mortality were performed. Plasma concentrations of MOV and NHC were determined on Study Day 5.

All animals survived to study termination and were sacrificed without necropsy following the last blood sample collection.

The TK parameters are presented in [Table 2.6.6: 31] and [Table 2.6.6: 32].

Table 2.6.6: 31 Mean Plasma MOV TK Parameters in Male Crl:CD(SD) and F344/NHsd Rats Following Oral Dosing of MOV: Study Day 5 (TT #[redacted]-1015)

Dose (mg/kg/day)	Group	Strain	Parameter	Units	Sex: Male	
					Mean	SE
50	1	Crl:CD(SD)	$AUC_{0\text{-}24hr}$	hr*µM	0.149	0.0275
			C_{max}	µM	0.0780	0.00696
			T_{max}	hr	0.500	NC
150	2	Crl:CD(SD)	$AUC_{0\text{-}24hr}$	hr*µM	0.362	0.0260
			C_{max}	µM	0.264	0.0130
			T_{max}	hr	0.500	NC
500	3	Crl:CD(SD)	$AUC_{0\text{-}24hr}$	hr*µM	1.89	0.201
			C_{max}	µM	1.04	0.156
			T_{max}	hr	0.500	NC
50	4	F344/NHsd	$AUC_{0\text{-}24hr}$	hr*µM	0.103	0.0120
			C_{max}	µM	0.0849	0.00582
			T_{max}	hr	0.500	NC
150	5	F344/NHsd	$AUC_{0\text{-}24hr}$	hr*µM	0.475	0.0308
			C_{max}	µM	0.282	0.00976
			T_{max}	hr	0.500	NC
500	6	F344/NHsd	$AUC_{0\text{-}24hr}$	hr*µM	2.00	0.141
			C_{max}	µM	1.11	0.0377
			T_{max}	hr	0.500	NC

$AUC_{0\text{-}24hr}$=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; NC Not Calculated; SE=standard error; T_{max}= time of maximum concentration.

Table 2.6.6: 32 Mean Plasma NHC Toxicokinetic Parameters in Male Crl:CD(SD) and F344/NHsd Rats Following Oral Dosing of MOV: Study Day 5 (TT #[redacted]-1015)

Dose (mg/kg/day)	Group	Strain	Parameter	Units	Sex: Male	
					Mean	SE
50	1	Crl:CD(SD)	$AUC_{0\text{-}24hr}$	hr*µM	14.8	1.98
			C_{max}	µM	6.70	1.01
			T_{max}	hr	0.500	NC
150	2	Crl:CD(SD)	$AUC_{0\text{-}24hr}$	hr*µM	57.6	7.37
			C_{max}	µM	23.4	3.20
			T_{max}	hr	0.500	NC
500	3	Crl:CD(SD)	$AUC_{0\text{-}24hr}$	hr*µM	302	45.0
			C_{max}	µM	101	15.2
			T_{max}	hr	1.00	NC
50	4	F344/NHsd	$AUC_{0\text{-}24hr}$	hr*µM	6.50	0.357
			C_{max}	µM	4.53	0.321
			T_{max}	hr	0.500	NC
150	5	F344/NHsd	$AUC_{0\text{-}24hr}$	hr*µM	29.8	1.93
			C_{max}	µM	20.9	2.16
			T_{max}	hr	0.500	NC
500	6	F344/NHsd	$AUC_{0\text{-}24hr}$	hr*µM	159	14.5
			C_{max}	µM	99.0	9.70
			T_{max}	hr	0.500	NC

$AUC_{0\text{-}24hr}$=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; NC Not Calculated; SE=standard error; T_{max}= time of maximum concentration.

In male Crl:CD(SD) rats, mean plasma MOV $AUC_{0\ 24hr}$ values were generally dose proportional between 50 and 150 mg/kg/day, but were slightly greater than dose proportional between 150 and 500 mg/kg/day. Mean plasma MOV C_{max} values were greater than dose proportional between 50 and 500 mg/kg/day. Mean plasma NHC $AUC_{0\ 24hr}$ and C_{max} values were greater than dose proportional between 50 and 500 mg/kg/day. In male F344/NHsd rats, mean plasma MOV and NHC $AUC_{0\ 24hr}$ and C_{max} values were greater than dose proportional between 50 and 500 mg/kg/day.

Mean plasma MOV $AUC_{0\ 24hr}$ and C_{max} values in F344/NHsd rats were generally similar to those achieved in Crl:CD(SD) rats, except at 50 mg/kg/day, when the mean $AUC_{0\ 24hr}$ value in F344/NHsd rats was slightly lower (0.69 times) than that achieved in Crl:CD(SD) rats. Mean plasma NHC $AUC_{0\ 24hr}$ values in F344/NHsd rats were generally lower (0.44 to

0.53 times) than those achieved in Crl:CD(SD) rats, and the mean NHC C_{max} value at 50 mg/kg/day in F344/NHsd rats was slightly lower (0.68 times) than that achieved in Crl:CD(SD) rats; however, mean NHC C_{max} values at 150 and 500 mg/kg/day were similar in both rat strains.

8.7.2.3 Exploratory Oral 14-Day Tolerability and Toxicokinetic Study in Nonpregnant Rabbits (TT #[redacted]-7043)

The objectives of this study [Sec. 2.6.7: 17C] were to determine the tolerability of MOV in nonpregnant rabbits after oral administration once daily for 14 days, to evaluate the TK profile of MOV and NHC on Study Day 7, and to evaluate hematology parameters on SD 15, in order to support dose selection for a pEFD study in rabbits (TT #[redacted]-7064) [Sec. 2.6.6: 6.2.3].

Fifteen female Dutch Belted rabbits (approximately 28 weeks of age) were assigned to 5 groups of 3 animals each. The rabbits were administered 3, 30, 300, or 1000 mg/kg/day of MOV in the vehicle (1.0% [w/v] methylcellulose in deionized water) or vehicle only, once daily by oral gavage. The dosing volume for all animals was 5 mL/kg.

Assessment of tolerability was based on mortality, clinical observations, body weights, food consumption, and evaluation of hematology parameters. Plasma MOV and NHC concentrations were determined in samples from treated rabbits.

All rabbits survived until scheduled study termination. There were no MOV-related clinical signs.

In the 1000 mg/kg/day group, there were MOV-related body weight losses (an average of -36 g between Study Days 1 and 15, compared to +75 g in controls) and unsatisfactory food consumption.

In the 3, 30, and 300 mg/kg/day groups, there were no MOV-related effects on mean body weight or food consumption, compared to controls.

There were no MOV-related alterations in hematology parameters.

The Study Day 7 TK parameters are presented in [Table 2.6.6: 33] and [Table 2.6.6: 34].

Table 2.6.6: 33 Mean Plasma MOV TK Parameters in Non-Pregnant Female Rabbits Following Oral Dosing of MOV: Study Day 7 (TT #[redacted]-7043)

Dose (mg/kg/day)	Group	Parameter	Units	Sex: Female	
				Mean	SE
3	2	AUC_{0-24hr}	hr*µM	NC[a]	NC[a]
		C_{max}	µM	0.0187	0.00777
		T_{max}	hr	17.3	6.67
30	3	AUC_{0-24hr}	hr*µM	0.155	0.0445
		C_{max}	µM	0.0124	0.00314
		T_{max}	hr	10.7	6.89
300	4	AUC_{0-24hr}	hr*µM	0.547	0.0739
		C_{max}	µM	0.131	0.0326
		T_{max}	hr	0.667	0.167
1000	5	AUC_{0-24hr}	hr*µM	1.01	NC[b]
		C_{max}	µM	0.275	0.0257
		T_{max}	hr	0.500	0.00

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; SE standard error; T_{max} time of maximum concentration.

NC[a] Not calculated due to limited number of concentration values that were greater than the lower limit of quantitation.

NC[b] Not calculated as there were only 2 animals available for the assessment (no sample could be obtained from one animal at 24 hr postdose. The value was not included in group mean calculations for MOV because the 24 hr sample appears to contribute to significant exposure for this analyte).

Table 2.6.6: 34 Mean Plasma NHC TK Parameters in Non-Pregnant Female Rabbits Following Oral Dosing of MOV: Study Day 7 (TT #[redacted]-7043)

Dose (mg/kg/day)	Group	Parameter	Units	Sex: Female	
				Mean	SE
3	2	$AUC_{0\text{-}24hr}$	hr*µM	3.03	0.177
		C_{max}	µM	1.80	0.431
		T_{max}	hr	0.833	0.167
30	3	$AUC_{0\text{-}24hr}$	hr*µM	30.7	1.92
		C_{max}	µM	17.2	1.67
		T_{max}	hr	0.500	0.00
300	4	$AUC_{0\text{-}24hr}$	hr*µM	423	24.1
		C_{max}	µM	165	20.9
		T_{max}	hr	1.33	0.333
1000	5	$AUC_{0\text{-}24hr}$	hr*µM	2,210	195[a]
		C_{max}	µM	578	39.4
		T_{max}	hr	1.33	0.333

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; SE standard error; T_{max} time of maximum concentration.

a No sample could be obtained from one animal at 24 hours postdose. The value was included in group mean calculations for NHC, as it was determined to have no substantive impact on the calculation.

Mean plasma MOV $AUC_{0\ 24hr}$ was not assessed at 3 mg/kg/day because many samples were below the LLOQ. Mean plasma MOV $AUC_{0\ 24hr}$ values were generally less than dose-proportional between 30 and 1000 mg/kg/day; while mean plasma MOV C_{max} values were similar between 3 and 30 mg/kg/day, and generally increased in a dose-proportional manner between 30 and 1000 mg/kg/day.

Mean plasma NHC $AUC_{0\ 24hr}$ values were dose-proportional between 3 and 30 mg/kg/day doses of MOV, and greater than dose-proportional between 30 and 1000 mg/kg/day doses. Mean plasma NHC C_{max} values were dose-proportional across all MOV doses.

In summary, all animals survived until scheduled study termination. MOV-related effects consisted of mean body weight loss and unsatisfactory food consumption at 1000 mg/kg/day.

8.7.2.4 Exploratory 16-Day Oral Toxicokinetic Study in Dogs (TT #[redacted]-1005)

The purpose of this study was to determine the TK profile of MOV and NHC when administered orally to dogs either daily or every 3 days for 16 days [Sec. 2.6.7: 17C].

Beagle dogs were assigned to 2 groups of 3 females or 3 males each that received 6 mg/kg/day (Dose Group 1) or 17 mg/kg every three days (Dose Group 2) of MOV in 1% methylcellulose at a dose volume of 2 mL/kg.

Daily observations for mortality were performed. Hematology evaluations were conducted pretest and on Study Day 16. Plasma samples were assayed for concentrations of MOV and NHC on Study Days 1 and 16. Peripheral blood mononuclear cells were assayed for concentrations of NHC-TP on Study Days 1 and 16.

All animals survived to study termination. There were no test article-related findings. The TK parameters are presented in [Table 2.6.6: 35] through [Table 2.6.6: 41].

Table 2.6.6: 35 Mean Plasma MOV TK Parameters in Dogs Following Oral Dosing of MOV: Study Day 1 (TT #[redacted]-1005)

				Sex			
				Female		Male	
Dose	Group	Parameter	Units	Mean	SE	Mean	SE
6 mg/kg/day	1	$AUC_{0\text{-}24hr}$	hr*µM	NC	NC		
		C_{max}	µM	0.294	0.0461		
		T_{max}	hr	0.500	0.00		
17 mg/kg/Q3D	2	$AUC_{0\text{-}72\ hr}$ [a]	hr*µM			1.12	NC
		C_{max}	µM			1.15	0.387
		T_{max}	hr			0.500	0.00

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; $AUC_{0\text{-}72hr}$ area under the concentration time curve from time 0 to 72 hours; C_{max} maximum concentration; NC Not calculated due to insufficient data for the calculation (less than 3 consecutive concentration values greater than LLOQ in concentration versus time profiles); SE standard error; Q3D every 3 days; T_{max} time of maximum concentration.

a N 1 due to insufficient data from the other 2 animals in the treatment cohort (less than 3 concentrations greater than LLOQ in concentration versus time profiles)

Table 2.6.6: 36 Mean Plasma MOV TK Parameters in Dogs Following Oral Dosing of MOV: Study Day 16 (TT #[redacted]-1005)

				Sex			
				Female		Male	
Dose	Group	Parameter	Units	Mean	SE	Mean	SE
6 (mg/kg/day)	1	$AUC_{0\text{-}24\ hr}$[a]	hr*µM	0.280	NC		
		C_{max}	µM	0.240	0.108		
		T_{max}	hr	0.500	0.00		
17 (mg/kg/Q3D)	2	$AUC_{0\text{-}72\ hr}$[a]	hr*µM			1.71	NC
		C_{max}	µM			1.41	0.849
		T_{max}	hr			0.500	0.00

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; $AUC_{0\text{-}72hr}$ area under the concentration time curve from time 0 to 72 hours; C_{max} maximum concentration; NC Not calculated due to insufficient data for the calculation (less than 3 consecutive concentration values greater than LLOQ in concentration versus time profiles); SE standard error; Q3D every 3 days; T_{max} time of maximum concentration.

a N 1 due to insufficient data from the other 2 animals in the treatment cohort (less than 3 concentrations greater than LLOQ in concentration versus time profiles)

Table 2.6.6: 37 Mean Plasma NHC TK Parameters in Dogs Following Oral Dosing of MOV: Study Day 1 (TT #[redacted]-1005)

				Sex			
				Female		Male	
Dose	Group	Parameter	Units	Mean	SE	Mean	SE
6 mg/kg/day	1	$AUC_{0\text{-}24\ hr}$	hr*µM	10.3	0.812		
		C_{max}	µM	6.51	0.695		
		T_{max}	hr	0.500	0.00		
17 mg/kg/Q3D	2	$AUC_{0\text{-}72\ hr}$	hr*µM			37.0	1.50
		C_{max}	µM			23.8	3.20
		T_{max}	hr			0.500	0.00

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; $AUC_{0\text{-}72hr}$ area under the concentration time curve from time 0 to 72 hours; C_{max} maximum concentration; Q3D every 3 days SE standard error; T_{max} time of maximum concentration.

Table 2.6.6: 38 Mean Plasma NHC TK Parameters in Dogs Following Oral Dosing of MOV: Study Day 16 (TT #[redacted]-1005)

				Sex			
				Female		Male	
Dose (mg/kg/day)	Group	Parameter	Units	Mean	SE	Mean	SE
6 (mg/kg/day)	1	$AUC_{0\text{-}24\ hr}$	hr*µM	9.54	0.987		
		C_{max}	µM	6.04	0.613		
		T_{max}	hr	0.500	0.00		
17 (mg/kg/Q3D)	2	$AUC_{0\text{-}72\ hr}$	hr*µM			34.1	1.77
		C_{max}	µM			21.5	2.59
		T_{max}	hr			0.500	0.00

$AUC_{0\text{-}24hr}$ area under the concentration time curve from time 0 to 24 hours; $AUC_{0\text{-}72hr}$ area under the concentration time curve from time 0 to 72 hours; C_{max} maximum concentration; Q3D every 3 days SE standard error; T_{max} time of maximum concentration.

Table 2.6.6: 39 Mean Peripheral Blood Mononuclear Cell (PBMC) NHC-TP Concentrations in Dogs Following Oral Dosing of MOV: Study Day 1 (TT #[redacted]-1005)

Dose	Group	Mean (± SE) Concentrations pmol/10^6 cells			
		0.5 hr	2 hrs	24 hrs	72 hrs
6 mg/kg/day	1	3.68 ± 0.476	3.81 ± 0.437	1.14 ± 0.129	NC
17 mg/kg/Q3D	2	4.49 ± 0.814	6.39 ± 0.625	2.19 ± 0.124	NC[a]

NC Not calculated; no samples collected for analysis as per protocol; NHC TP N hydroxycytidine 5´ triphosphate (EIDD 2061); Q3D every 3 days; ; SE standard error

NC[a] Not calculated as sample exceeded short term stability for analysis of NHC TP

Table 2.6.6: 40 Mean Peripheral Blood Mononuclear Cell (PBMC) NHC-TP Concentrations in Dogs Following Oral Dosing of MOV: Study Day 7 (TT #[redacted]-1005)

Dose	Group	Mean (± SE) Concentrations pmol/10^6 cells
		72 hrs
17 mg/kg/Q3D	2	0.534 ± NC

NC Not calculated; less than 3 sample values available for the calculation; NHC TP N hydroxycytidine 5´ triphosphate (EIDD 2061); Q3D every 3 days; ; SE standard error

Table 2.6.6: 41 Mean Peripheral Blood Mononuclear Cell (PBMC) NHC-TP Concentrations in Dogs Following Oral Dosing of MOV: Study Day 16 (TT #[redacted]-1005)

Dose	Group	Mean (± SE) concentration pmol/10^6 cells			
		0.5 hr	2 hrs	24 hrs	72 hrs
6 mg/kg/day	1	6.43 ± 0.569	6.57 ± 0.772	1.96 ± 0.306	NC
17 mg/kg/Q3D	2	5.18 ± 0.844	9.93 ± 3.24	2.65 ± 0.321	1.02 ± NC[a]

NC Not calculated; no samples collected for analysis as per protocol; Q3D every 3 days; SE standard error
NC[a] Not calculated; less than 3 sample values available for the calculation

After repeated oral dosing of MOV, mean plasma MOV and NHC $AUC_{0\ 24hr}$ (6 mg/kg/day), $AUC_{0\ 72hr}$ (17 mg/kg/Q3D) and C_{max} values were similar to those achieved on Study Day 1, demonstrating that steady state exposures were generally achieved following the first dose, with no apparent accumulation or loss of exposure after repeated dosing. Mean plasma NHC $AUC_{0\ 24hr}$, $AUC_{0\ 72hr}$ and C_{max} values were approximately 15 to 34 times those achieved after respective dosing for MOV.

NHC-TP was detected in PBMCs after MOV dosing at 6 mg/kg/day and 17 mg/kg/Q3D. Highest PBMC NHC-TP concentrations were observed at 2 hours after MOV dosing for both dosing regimens. At 6 mg/kg/day, mean NHC-TP concentrations in PBMCs were less than 2-fold higher on Study Day 16 than those attained on Study Day 1. At 17 mg/kg/Q3D, mean PBMC NHC-TP concentrations on Study Day 16 were generally similar to those achieved on Study Day 1. Mean PBMC NHC-TP concentrations following 17 mg/kg/Q3D were generally similar (i.e., within 2-fold) to those achieved at 6 mg/kg/day at respective times.

8.7.3 Other Studies

8.7.3.1 A 7-Day In Vivo Mammalian Dose Range Finder Assay in Fischer 344 Male Rats (TT #[redacted]-9027)

This study assessed the tolerability of MOV in Fischer 344 WT:F344/NHsd male rats, the rat strain used in the in vivo mutation assay at the c*II* locus in Big Blue® transgenic F344 rats (TT #[redacted]-9025) [Sec. 2.6.6: 4.2.3], at doses up to 500 mg/kg/day [Sec. 2.6.7: 17D], the highest dose tested in a previous 1-month toxicity study in Sprague Dawley Rats (TT #[redacted]-7814) [Sec. 2.6.6: 3.2.2]. Fischer 344 rats were assigned to 3 groups of 3 males each that received 250 or 500 mg/kg/day of MOV in 1% methylcellulose in deionized water or vehicle only for 7 days, at a dose volume of 10 mL/kg by oral gavage.

Assessment of tolerability was based on mortality, clinical observations, body weights, food consumption, and clinical pathology evaluations. Plasma test article concentrations were determined on Study Day 7.

No mortality was noted. All animals survived until the end of the assay. Ruffled fur was observed in all animals at 250 and 500 mg/kg/day beginning on Study Day 5 and hunched posture was seen in one animal at 500 mg/kg/day beginning on Study Day 6. There were no

notable changes in food consumption and body weight. Compared to controls, there were very slight, statistically significantly, decreases in mean RBC, HGB, and HCT at 250 mg/kg/day (-10% to -12%) and 500 mg/kg/day (-16 to -17%) on Day 8. These changes may represent test article-related effects but it should be noted that the greater blood volume collected from these groups (and not from controls) on Day 7 for bioanalysis likely contributed to these lower values. The toxicokinetic parameters are presented in [Table 2.6.6: 42] and [Table 2.6.6: 43].

Table 2.6.6: 42 Mean Plasma MOV TK Parameters in Rats Following Oral Dosing of MOV: Study Day 7 (TT #[redacted]-9027)

				Sex: Male	
Dose (mg/kg/dose)	**Group**	**Parameter**	**Units**	**Mean**	**SE**
250	2	AUC_{0-24hr}	hr*µM	0.228	0.00653
		C_{max}	µM	0.0923	0.00364
		T_{max}	hr	1.00	NC
500	3	AUC_{0-24hr}	hr*µM	0.590	0.0782
		C_{max}	µM	0.230	0.0144
		T_{max}	hr	1.00	NC

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration

Table 2.6.6: 43 Mean Plasma NHC TK Parameters in Rats Following Oral Dosing of MOV: Study Day 7 (TT #[redacted]-9027)

				Sex: Male	
Dose (mg/kg/dose)	**Group**	**Parameter**	**Units**	**Mean**	**SE**
250	2	AUC_{0-24hr}	hr*µM	133	7.35
		C_{max}	µM	60.6	3.86
		T_{max}	hr	1.00	NC
500	3	AUC_{0-24hr}	hr*µM	233	50.8
		C_{max}	µM	91.8	25.4
		T_{max}	hr	1.00	NC

AUC_{0-24hr} area under the concentration time curve from time 0 to 24 hours; C_{max} maximum concentration; NC Not Calculated; SE standard error; T_{max} time of maximum concentration

Based on results of this study, 500 mg/kg/day of MOV was tolerated for 7 days of dosing in male Fischer 344 rats.

8.7.3.2 In-Life Only: In Vivo Mutation Assay at the *cII* Locus in Big Blue® Transgenic F344 Rats (TT #[redacted]-9047)

The purpose of this study was to determine the effect of MOV on mutant frequency at the *cII* gene in testes from male transgenic Fischer 344 Big Blue® rats [Sec. 2.6.7: 17D]. The supporting Big Blue® mutation analysis portion of the study was not completed based on the negative results in somatic cells from liver and bone marrow in another study in Big Blue® transgenic F344 rats (TT #[redacted]-9025) [Sec. 2.6.6: 4.2.3]; therefore, only relevant study design and in-life results are presented below.

MOV was administered at doses of 0 (vehicle control), 50, 150 and 500 mg/kg/day, to six males/group. The vehicle was 1 % methylcellulose in deionized water. Test article and vehicle control formulations were administered once daily by oral gavage for 28 consecutive days, at a dose volume of 10 mL/kg. The high dose of 500 mg/kg/day was selected based on clinical signs, including hunched posture and ruffled fur, and hematological changes observed in Fischer 344 rats orally administered MOV at 500 mg/kg/day for 7 days in a dose range-finding study (TT #[redacted]-9027) [Sec. 2.6.6: 8.7.3.1]. The positive control animals were dosed via oral gavage on Days 1, 2, 3, 12, 19 and 26 with 20 mg/kg/day of *N*-ethyl-*N*-nitrosourea formulated in phosphate buffer solution, pH 6.00. ENU was also administered at a dose volume of 10 mL/kg.

Assessment of tolerability was based on mortality, clinical observations, body weights, and food consumption. Animals were sacrificed by CO_2 overdose on Day 56. At necropsy, the right testis, liver (right medial lobe), and bone marrow also were collected for possible mutant analysis.

There were no unscheduled deaths. A decrease in mean body weight gain was noted at 500 mg/kg/day (-12% difference compared to the vehicle control group). There were no notable changes in food consumption.

8.7.3.3 7-Day Repeat-Dose Tolerability of MOV Following Oral Doses to Rhesus Monkeys (TT #[redacted]-7817)

The purpose of this study was to evaluate the toxicity and tolerability of MOV in male and female rhesus monkeys when administered escalating doses of 150, 300, and 500 mg/kg/day for 7 consecutive days per dose level (Phases 1, 2, and 3, respectively) with 7 days between each dose level [Sec. 2.6.7: 17D].

Assessment of toxicity and tolerability was based on mortality, clinical observations, body weights, food consumption, and clinical pathology.

Administration of MOV at doses up to 500 mg/kg/day was well tolerated, with no test article-related mortality, or changes in body weight, food consumption, or clinical pathology. MOV-related clinical observations included occasional nonformed and/or liquid feces in males administered ≥300 mg/kg/day and females administered 300 mg/kg/day.

Toxicokinetic parameters for NHC are presented in [Table 2.6.6: 44] through [Table 2.6.6: 46].

Table 2.6.6: 44 Plasma TK Parameters of NHC in Rhesus Monkey Plasma after Oral Doses of MOV at 150 mg/kg/day, data shown as Mean (N 3 for individual sexes) (TT #[redacted]-7817)

Animal Group	Day	C_{max} (µM)	AUC_{inf} (µM*hr)	Tmax (hr)	t1/2 (hr)
Male	1	23.2	42.1	1.0	0.93
Female	1	27.7	57.3	1.3	0.61
Male	7	28.7	41.1	1.3	0.39
Female	7	31.5	51.6	1.3	0.51

AUCinf area under the time concentration curve extrapolated to infinity; Cmax maximum concentration; hr hour(s); N Number; NHC EIDD 1931 or N hydroxycytidine; t1/2 terminal half life; TK toxicokinetic; Tmax time to maximum concentration

Table 2.6.6: 45 Plasma TK Parameters of NHC in Rhesus Monkey Plasma after Oral Doses of MOV at 300 mg/kg/day, data shown as Mean (N 3 for individual sexes) (TT #[redacted]-7817)

Animal Group	Day	C_{max} (µM)	AUC_{inf} (µM*hr)	Tmax (hr)	t1/2 (hr)
Male	1	88.5	132.1	1.3	1.9
Female	1	70.7	141.7	2.0	1.2
Male	7	70.0	129.2	1.0	2.24
Female	7	134.9	229.9	1.7	1.36

AUCinf area under the time concentration curve extrapolated to infinity; Cmax maximum concentration; N Number; NHC EIDD 1931 or N hydroxycytidine; t1/2 terminal half life; TK toxicokinetic; Tmax time to maximum concentration

Table 2.6.6: 46 Plasma TK Parameters of NHC in Rhesus Monkey Plasma after Oral Doses of MOV at 500 mg/kg/day, data shown as Mean (N 3 for individual sexes) (TT #[redacted]-7817)

Animal Group	Day	C_{max} (µM)	AUC_{inf} (µM*hr)	Tmax (hr)	t1/2 (hr)
Male	1	222.7	338.1	1.3	2.6
Female	1	59.8	180.3	1.3	1.7
Male	7	146.7	302.4	1.7	2.09
Female	7	115.9	246.4	1.7	2.82

AUCinf area under the time concentration curve extrapolated to infinity; Cmax maximum concentration; hr hour(s); N Number; NHC EIDD 1931 or N hydroxycytidine; t1/2 terminal half life; TK toxicokinetic; Tmax time to maximum concentration

Plasma concentrations of MOV were quantifiable in all animals at 0.5 hours postdose, indicating that MOV was readily absorbed following single and multiple oral doses.

However, no meaningful toxicokinetic parameters could be established for MOV due to very low systemic exposure.

Plasma concentrations of NHC were quantifiable in all animals at 0.5 hours postdose, indicating NHC was readily formed following single and multiple oral doses of MOV. Following a single oral dose of 150, 300, or 500 mg/kg/day of MOV, exposure (according to C_{max} and AUC_{inf}) to NHC generally increased. Following multiple oral doses of 150, 300, or 500 mg/kg/day, little to no systemic accumulation of NHC was observed. Peak and total exposures to NHC were generally similar (<2-fold difference) in males and females.

9 DISCUSSION AND CONCLUSIONS

MOV was evaluated in a comprehensive toxicology program including genotoxicity assays (including Ames assays, in vitro and in vivo micronucleus assays, an in vivo Pig-a assay in rats, and an in vivo mutation assay in Big Blue® transgenic rats), tolerability/DRF studies in mice, rats, and dogs, repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs, fertility studies in male and female rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a pre- and post-natal developmental toxicity study in rats. Additional non pivotal short-term tolerability and/or TK studies were conducted in mice, rats, rabbits, and monkeys.

The MOV $AUC_{0\ 24hr}$ exposure multiples were not calculated given that MOV is rapidly hydrolyzed to NHC and is generally undetectable in human plasma (LLOQ of 0.0152 µM). The C_{max} at the NOAEL in rat (150 mg/kg/day) and dog (6 mg/kg/day) of 0.557 µM and 0.42 µM, respectively are much higher than the human plasma concentrations, which are generally below the LLOQ of 0.0152 µM.

NHC systemic $AUC_{0\ 24hr}$ exposure multiples are shown in [Table 2.6.6: 47].

Table 2.6.6: 47 NHC Systemic Exposure Multiples

Species	Study Duration or Study Type	Dose Levels (mg/kg/day)	$AUC_{0\text{-}24hr}$ (µM*hr) (F/M)[a]	Exposure Multiple Relative to 800 mg Q12H Clinical Dose[b] (F/M)
Repeat-Dose Toxicity				
Mouse (Wild-Type CByB6F1 Tg(HRAS) 2Jic)	1-Month[c] (TT #[redacted]-7825)	100	29.6	0.4
		300 (NOAEL)	76.8	1.0
		700	236	3.1
		2000	1420	19

Species	Study Duration or Study Type	Dose Levels (mg/kg/day)	$AUC_{0\text{-}24hr}$ (µM*hr) (F/M)[a]	Exposure Multiple Relative to 800 mg Q12H Clinical Dose[b] (F/M)
Rat	1-Month (TT #[redacted]-7814)	50	9.7/21	0.1/0.3
		150	42/108	0.6/1.4
		500 (NOAEL)	319/590	4.2/7.8
	3-Month (TT #[redacted]-1014)	150 (M only) (NOAEL for M)	52.2	0.7
		200 (F only)	67.6	0.9
		500 (NOAEL for F)	250/408	3.3/5.4
		1000	706/1120	9.3/15
Dog	1-Month (TT #[redacted]-7815)	6 (NOAEL)	9.5	0.1
		17	29.7	0.4
		50	118.8	1.6
Reproductive and Developmental Toxicity				
Rat	Fertility (TT #[redacted]-9000, TT #[redacted]-9012)	100	14.9/45.6	0.2/0.6
		250	61.4/179	0.8/2.4
		500 (NOAEL for general toxicity and fertility - F & M)	157/463	2.1/6.1
	EFD (TT #[redacted]-7000)	100	18.4	0.2
		250 (NOAEL for maternal and developmental toxicity)	58.3	0.8
		500	217[d]	2.9
		1000[e]	570[f]	7.5
Rabbit	EFD (TT #[redacted]-7010)	125 (NOAEL for maternal toxicity)	111	1.5
		400 (NOAEL for developmental toxicity)	490	6.5
		750	1360	18
Rat	PPND (TT #[redacted]-9010)	100	9.12	0.1
		250	62.6	0.8
		500 (NOAEL for maternal and F_1 generation toxicity)	122	1.6

AUC area under the concentration time curve; $AUC_{0\text{-}24hr}$ AUC from time 0 to 24 hours; F female; GD Gestation Day; M male; NC Not calculated; NHC EIDD 1931 or N hydroxycytidine; NOAEL no observed adverse effect level; Q12H every 12 hours.

a Data presented as sexes combined (Wild Type CByB6F1 Tg(HRAS)2Jic mice), F/M (repeat dose rat and dog toxicity studies) or females only (pEFD and EFD toxicity studies).

Species	Study Duration or Study Type	Dose Levels (mg/kg/day)	$AUC_{0\text{-}24hr}$ (µM*hr) (F/M)[a]	Exposure Multiple Relative to 800 mg Q12H Clinical Dose[b] (F/M)

b $AUC_{0\text{-}24hr}$ exposure multiples were calculated using clinical exposures of 75.6 µM*hr at 800 mg Q12H, based on population PK estimates of exposure in COVID 19 patients from Part 1 of P001/P002.

c Exposures for the 28 day toxicity study in Wild Type CByB6F1 Tg(HRAS)2Jic mice (TT # [redacted] 9037) were obtained from the 7 day TK study in Wild Type CByB6F1 Tg(HRAS)2Jic mice (TT # [redacted] 9011).

d Value is from the GLP pEFD rat study (TT # [redacted] 7054). Due to inaccurate plasma sample volumes collected 0.5, 1, 2 and 4 hours postdose at 500 mg/kg/day, no AUC0 24 hr value could be calculated for that dose group in the definitive EFD rat study (TT # [redacted] 7000).

e Dose used in the GLP pEFD rat study only (TT # [redacted] 7054). Due to maternal toxicity including mortality, the dose of 1000 mg/kg/day was not selected for the definitive EFD study; the high dose of the definitive EFD rat study (TT # [redacted] 7000) was 500 mg/kg/day.

f Value from the GLP pEFD rat study (TT # [redacted] 7054).

Below, NHC exposure multiples were calculated relative to the clinical exposure at the human dose of 800 mg Q12H, corresponding to NHC exposure of 75.6 µM*hr (based on population PK estimates of exposure in COVID-19 patients from P001/P002).

Genotoxicity/mutagenicity risk assessment: The integrated assessment of the mutagenic and genotoxic potential of MOV detailed in [Sec. 2.6.6: 4] indicates that MOV is not mutagenic or genotoxic in in vivo mammalian systems. Based on the totality of the genotoxicity data, MOV is of low risk of genotoxicity in clinical use.

Target Organs of Toxicity: Target organs of toxicity identified in the GLP repeat-dose toxicity studies included bone marrow in dogs only, and growth plate in rats only. In addition, gastrointestinal toxicity and liver enzyme elevations were noted in the rat and dog 7-day tolerability studies at doses that exceeded the MTDs, 2000 mg/kg/day in rats and ≥300 mg/kg/day in dogs.

Bone marrow/hematopoietic findings: In the 28-day repeat-dose toxicity study in dogs (doses of 6, 17, and 50 mg/kg/day), mild dose-related hematologic findings affecting all cell lines were observed following 7 days of dosing. More severe hematologic changes were apparent after 14 to 21 days of continuous dosing leading to pancytopenia, including severe thrombocytopenia and associated hemorrhage at 17 mg/kg/day (0.4-fold the clinical NHC exposure at 800 mg Q12H) and 50 mg/kg/day (2-fold the clinical NHC exposure at 800 mg Q12H). This resulted in early termination of treatment at 50 mg/kg/day after 2 weeks of dosing and at 17 mg/kg/day after 3 weeks of dosing. These hematologic changes were secondary to decreased cellularity of the bone marrow hematopoietic precursors (bone marrow depletion) observed at postmortem examinations. The hematopoietic changes were fully reversible at 17 mg/kg/day with essentially normal bone marrow and hematologic parameters following a 1-month recovery period. Animals in the 50 mg/kg/day group were euthanized approximately 10 days after treatment termination; hematopoietic changes were partially reversible during the shortened recovery period. Only minor, reversible, nonadverse hematopoietic changes were seen in animals administered 6 mg/kg/day for 28 days. The

NOAEL in dogs was therefore 6 mg/kg/day (0.13-fold the clinical NHC exposure at 800 mg Q12H).

The bone marrow/hematopoietic findings are of low risk in humans based on the following:

- Hematological changes observed after 7 days of dosing in dogs in the 28-day study were relatively mild compared with later time points and the hematopoietic and hematologic changes demonstrated reversibility upon discontinuation of treatment.
- The proposed duration for treatment of COVID-19 is 5 days, and the clinical safety database shows no hematological effects indicative of bone marrow toxicity.
- There were no hematopoietic findings in rats dosed for 3 months up to 1000 mg/kg/day (9.3/15-fold (female/male) the clinical NHC exposure at 800 mg Q12H), or in mice dosed for 1 month up to 2000 mg/kg/day (19-fold the clinical NHC exposure at 800 mg Q12H). There were no hematologic changes in female rabbits dosed for 2 weeks up to 1000 mg/kg/day (29-fold the clinical NHC exposure at 800 mg Q12H), or in rhesus monkeys dosed for 7 days up to 500 mg/kg/day (3.6-fold the clinical NHC exposure at 800 mg Q12H). Decreased hematology values, notably RETs (89%), white blood cells, and absolute lymphocyte counts (52%), were only observed at 2000 mg/kg/day in a 7-day rat DRF; (61/91-fold (female/male) the clinical NHC exposure at 800 mg Q12H).

Growth plate findings: Changes in the growth plate of bones were observed in the 3-month oral toxicity study in rats, in males at ≥500 mg/kg/day (5.4-fold the clinical NHC exposure at 800 mg Q12H) and in females at 1000 mg/kg/day (9.3-fold the clinical NHC exposure at 800 mg Q12H). The findings consisted of an increase in the thickness of the growth plate (physis), associated with decreased bone formation at the end of long bones in males at 1000 mg/kg/day and thickening of the growth cartilage of the epiphysis of long bones and in patella of males and females at 1000 mg/kg/day. Minimal thickening of epiphyseal growth cartilage was also observed in males at 500 mg/kg/day. There were no changes observed in remaining tissues in the femorotibial joint, including articular surfaces, ligaments, synovial tissue, other soft tissue, and the cortical bone. There were no growth plate findings in rats dosed for 1 month up to 500 mg/kg/day (4.2/7.8-fold (female/male) the clinical NHC exposure at 800 mg Q12H), in dogs dosed for up to 14 days at 50 mg/kg/day (1.6-fold the clinical NHC exposure at 800 mg Q12H), or in mice dosed for 1 month at doses up to 2000 mg/kg/day (19-fold the clinical NHC exposure at 800 mg Q12H).

These growth plate findings are not relevant to adult humans because growth plates are no longer present in the mature skeleton of adult humans. The growth plate findings (observed in rats after 3 months of treatment, but not after 1-month of dosing) are of unclear significance in the context of short duration treatment in children. The findings were noted in rapidly growing rats (5 to 6 weeks of age at study start) that approximately doubled their body weights over the study duration. This very rapidly bone growth cannot be directly translated to humans due to species-specific differences in skeletal development and bone turnover [Ref. 4.3: 05NK2R]. Additional cartilage findings observed only in the 3-month toxicity study in rats included a minimal to mild cytoplasmic alteration in chondrocytes of the tracheal cartilage in males only at ≥ 500 mg/kg/day. This change was not associated with

degenerative or inflammatory changes, did not impact the overall structure or integrity of the cartilage, did not impact airway size or diameter, and is consequently nonadverse. There were no growth plate or cartilage findings at 150 mg/kg/day in males (0.7-fold the clinical NHC exposure at 800 mg Q12H) and at 500 mg/kg/day in females (3.3-fold the clinical NHC exposure at 800 mg Q12H).

Gastrointestinal toxicity and liver enzyme elevations: Additional findings including GI findings (e.g., stomach distention, emesis, diarrhea) and liver enzyme elevations were noted in the 7-day tolerability studies at high doses that exceeded the MTDs (2000 mg/kg/day in rats, 61/91-fold (female/male) the clinical NHC exposure at 800 mg Q12H and ≥300 mg/kg/day in dogs (19-fold the clinical NHC exposure at 800 mg Q12H). Liver enzyme elevations consisted of ≤2-fold increases in ALT and/or AST in rats at 2000 mg/kg/day, as well as approximately 2-fold increases in AST at 300 mg/kg/day in dogs, and up to 5-fold increases in ALP and ALT and 30-fold increases in AST at 1000 mg/kg/day in dogs (66-fold the clinical NHC exposure at 800 mg Q12H).

Developmental and reproductive toxicity: In the female and male rat fertility studies, there were no MOV-related effects on fertility or early embryonic development up to the highest dose tested, 500 mg/kg/day (2.1/6.1-fold (female/male) the clinical NHC exposure at 800 mg Q12H). In pregnant rats administered MOV during the organogenesis period, developmental toxicity including embryolethality (post-implantation losses) and malformations/ teratogenicity was observed at 1000 mg/kg/day (7.5-fold the clinical NHC exposure at 800 mg Q12H) and reduced fetal growth at ≥500 mg/kg/day (≥2.9-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at doses up to 250 mg/kg/day (0.8-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight loss, resulting in the early sacrifice of individual animals at 1000 mg/kg/day and decreased body weight gain at ≥500 mg/kg/day. In pregnant rabbits, developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (18-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at up to 400 mg/kg/day (6.5-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight gain and abnormal fecal output at ≥400 mg/kg/day. In the pre- and postnatal development study in rats, there was no F0 maternal or F1 generation toxicity up to the highest dose evaluated of 500 mg/kg/day (1.6-fold the clinical NHC exposure at 800 mg Q12H). While embryolethality (post-implantation losses) and teratogenicity were limited to rats exposed to 7.5-fold the clinical NHC exposure at 800 mg Q12H during the organogenesis period, and these developmental findings were not observed in rats up to 2.9-fold the clinical NHC exposure at 800 mg Q12H or rabbits up to 18-fold the clinical NHC exposure at 800 mg Q12H, the use of MOV is conservatively not recommended during pregnancy. WOCBP should use effective contraception for the duration of treatment and for at least 4 days after the last dose.

Overall, the nonclinical safety profile supports the safe use of MOV for the treatment of COVID-19 in adult patients.

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Sec. 2.6.7.1 Toxicology: Overview

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day) [a]	GLP Compliance	Testing Facility	Study Number	CTD Location
Single-Dose Toxicity: Single dose toxicity was assessed in Phase A of the single dose MTD/7 day dose range finding studies in mice (TT # [redacted] 7850), rats (TT # [redacted] 7825) and dogs (TT # [redacted] 7826), and discussed under repeat dose toxicity.								
Repeat-Dose Toxicity								
Mouse								
NHC: 1 Day MTD (Phase A)	Mouse/Crl:CD1® (ICR)	Oral (gavage)	Phase A: 1 day (MTD) Phase A	500, 1000, 1500, 2000	Non GLP	[redacted] USA	TT # [redacted] 7850 [redacted]	[Ref. 4.2.3.2: TT [redacted] 7850FIN]
NHC: 7 Day (Phase B) Toxicity			Phase B: 7 Days	0, 200, 500, 1000				
28 Day (Dose Range Finding) Toxicity & TK	Mouse/Wild Type CByB6F1 Tg(HRAS)2Jic	Oral (gavage)	28 Days	0, 100, **300**, 700, 2000	GLP[b]	[redacted] USA	TT # [redacted] 9037 [redacted]	[Ref. 4.2.3.2: TT [redacted] 9037FIN]
Rat								
1 Day MTD (Phase A)	Rat/Hsd:SD	Oral (gavage)	Phase A: 1 day (MTD) Phase A	500, 1000, 1500, 2000	Non GLP	[redacted] USA	TT # [redacted] 7825 [redacted]	[Ref. 4.2.3.2: TT [redacted] 7825FIN]
7 Day (Phase B) Toxicity			Phase B: 7 Days	0, 200, 700, 2000				
28 Day Toxicity & TK with 14 Day Recovery Period	Rat/Hsd:SD	Oral (gavage)	28 Days	0, 50, 150, **500**	GLP	[redacted] USA	TT # [redacted] 7814 [redacted]	[Ref. 4.2.3.2: TT [redacted] 7814FIN]

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	CTD Location
Repeat-dose Toxicity (continued)								
3 Month Toxicity and TK	Rat/Crl:CD(SD)	Oral (gavage)	91 or 92 days	0, **150** (males only; **NOAEL for males**), 200 (females only), **500** (**NOAEL for females**), 1000	GLP	Merck Research Laboratories West Point, PA USA [c]	TT # [redacted] 1014	[Ref. 4.2.3.2: TT [redacted] 1014FIN]
Dog								
1 Day MTD (Phase A)	Dog (beagle)	Oral (gavage)	Phase A: 1 day (MTD) Phase A	300, 500, 1000, 2000 (Rising dose)	Non GLP	[redacted] USA	TT # [redacted] 7826 [redacted]	[Ref. 4.2.3.2: TT [redacted] 7826FIN]
7 Day (Phase B) Toxicity			Phase B: 7 Days	0, 100, 300, 1000				
28 Day Toxicity & TK with 28 Day Recovery Period	Dog (beagle)	Oral (gavage)	28 days[d]	0, **6**, 17, 50	GLP	[redacted] USA	TT # [redacted] 7815 [redacted]	[Ref. 4.2.3.2: TT [redacted] 7815FIN]
Genotoxicity								
NHC: Microbial Mutagenesis Assay	*Salmonella typhimurium* (TA1537, TA98, TA100, TA1535) and *Escherichia coli* (WP2 *uvrA*)	In vitro	~48 hrs	1.5 to 5000 µg/plate +/ S9	Non GLP	[redacted] USA	TT # [redacted] 7851 [redacted]	[Ref. 4.2.3.3.1: TT [redacted] 7851FIN]

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	CTD Location
Genotoxicity (continued)								
Microbial Mutagenesis Assay	*Salmonella typhimurium* (TA1537, TA98, TA100, TA102, TA1535) *and Escherichia coli* (WP2 *uvrA*)	In vitro	~48 hrs	25 to 5000 µg/plate (WP2 *uvrA* and TA102 ±S9); 1 to 1000 µg/plate (TA1537, TA98, TA100, TA1535 +S9); 50 to 5000 µg/plate (TA1537, TA98, TA100, TA1535 S9)	GLP [e]	[redacted] USA	TT # [redacted] 7810	[Ref. 4.2.3.3.1: TT [redacted] 7810FIN]
Micronucleus Induction Assay	TK6 cells	In vitro	~4 or 27 hrs	4 hr (without activation) 82.5, 165, 330 µg/mL; 4 hr (with activation) 2.58, 20.6, 124 µg/mL; 27 hr (without activation) 2.58, 61.9, 248 µg/mL	(GLP) [f]	[redacted] USA	TT # [redacted] 7806	[Ref. 4.2.3.3.1: TT [redacted] 7806FIN]
Micronucleus Induction Assay	Rat/Crl:CD(SD)	Oral (gavage)	2 days	0, 500, 1000, 2000	GLP [g]	[redacted] USA	TT # [redacted] 7816	[Ref. 4.2.3.3.2: TT [redacted] 7816FIN]
Mammalian Peripheral Blood Erythrocyte Pig a Mutation Assay	Rat/Crl:CD(SD)	Oral (gavage)	28 days	0, 50, 150, 500	GLP [h]	[redacted] Canada	TT # [redacted] 7808	[Ref. 4.2.3.3.2: TT [redacted] 7808FIN]

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	CTD Location
Genotoxicity (continued)								
In Vivo Mutation Assay at cII Locus	Rat (Big Blue® Transgenic F344)	Oral (gavage)	28 days	0, 50, 150, 500	GLP	[redacted] USA	TT # [redacted] 9025	[Ref. 4.2.3.3.2: TT [redacted] 9025FIN]
Carcinogenicity: No carcinogenicity studies have been completed.								
Reproductive and Developmental Toxicity								
Fertility (Female)	Rat/Crl:CD(SD)	Oral (gavage)	2 weeks prior to cohabitation through cohabitation and continuing to GD 7	0, 100, 250, **500**	GLP i	[redacted] USA	TT # [redacted] 9000	[Ref. 4.2.3.5.1: TT [redacted] 9000FIN]
Fertility (Male)	Rat/Crl:CD(SD)	Oral (gavage)	2 weeks prior to cohabitation through mating until 1 day prior to sacrifice (~6 weeks)	0, 100, 250, **500**	GLP i	[redacted] USA	TT # [redacted] 9012	[Ref. 4.2.3.5.1: TT [redacted] 9012FIN]
Preliminary Embryo fetal Developmental & TK	Rat/Crl:CD(SD)	Oral (gavage)	GD 6 17	0, 100, 200, 500, 1000	GLP j	Merck Research Laboratories West Point, PA USA	TT # [redacted] 7054	[Ref. 4.2.3.5.2: TT [redacted] 7054FIN]
Embryo fetal Developmental & TK	Rat/Crl:CD(SD)	Oral (gavage)	GD 6 17	0, 100, **250** (NOAEL for maternal and developmental toxicity), 500	GLP j	Merck Research Laboratories West Point, PA USA	TT # [redacted] 7000	[Ref. 4.2.3.5.2: TT [redacted] 7000FIN]

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	CTD Location
Reproductive and Developmental Toxicity (continued)								
Preliminary Embryo fetal Developmental & TK	Rabbit (Dutch Belted)	Oral (gavage)	GD 7 19	0, 60, 200, 500, 1000	GLP k	Merck Research Laboratories West Point, PA USA	TT # 7064	[Ref. 4.2.3.5.2: TT 7064FIN]
Embryo fetal Developmental & TK	Rabbit (Dutch Belted)	Oral (gavage)	GD 7 19	0, **125** (NOAEL for maternal toxicity), **400** (NOAEL for developmental toxicity), 750	GLP l	Merck Research Laboratories West Point, PA USA	TT # 7010	[Ref. 4.2.3.5.2: TT 7010FIN]
Pre and Postnatal Development & TK	Rat/Crl:CD(SD)	Oral (gavage)	GD 6 LD20	0, 100, 250, **500**	GLP m	USA	TT # 9010	[Ref. 4.2.3.5.3: TT 9010FIN]
Local Tolerance								
Bovine corneal opacity and permeability test	Isolated bovine corneas	In vitro	4 hrs	0.75 g	GLP n	USA	TT # 7801	[Ref. 4.2.3.6: TT 7801FIN]
MatTek Epiderm™ MTT Viability Assay	MatTek Epiderm™ tissue samples	In vitro	1, 4, or 24 hrs	100 mg	GLP n	USA	TT # 7802	[Ref. 4.2.3.6: TT 7802FIN]

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	CTD Location
Other Toxicity Studies (Immunotoxicity)								
Local Lymph Node Assay	Mouse (CBA J)	Topical	3 days	25% MOV solution,	GLP [n]	[redacted] USA	TT # [redacted] 7803	[Ref. 4.2.3.7.2: TT [redacted] 7803FIN]
Other Toxicity Studies (Photoreactivity)								
Photoreactivity assay Reactive Oxygen Species (ROS)	NA	In vitro	NA	200 µM	Non GLP	Merck Research Laboratories West Point, PA USA	TT # [redacted] 7814	[Ref. 4.2.3.7.7: TT [redacted] 7814FIN]
Other Toxicity Studies (Toxicokinetics)								
7 Day TK	Mouse/Wild Type CByB6F1 Tg(HRAS)2Jic	Oral (gavage)	7 days	100, 300, 700, 2000	GLP	[redacted] USA	TT # [redacted] 9011	[Ref. 4.2.3.7.7: TT [redacted] 9011FIN]
Exploratory 5 Day TK	Rat/ Crl:CD(SD); Rat/Fischer 344: F344/NHsd	Oral (gavage)	5 days	50, 150, 500,	Non GLP	Merck Research Laboratories West Point, PA USA	TT # [redacted] 1015	[Ref. 4.2.3.7.7: TT [redacted] 1015FIN]
Exploratory 14 Day Tolerability & TK (Nonpregnant)	Rabbit (Dutch Belted)	Oral (gavage)	14 days	0, 3, 30, 300, 1000	Non GLP	Merck Research Laboratories West Point, PA USA	TT # [redacted] 7043	[Ref. 4.2.3.7.7: TT [redacted] 7043FIN]
Exploratory 16 Day TK	Dog (beagle)	Oral (gavage)	16 days	6 (QD), 17 (Q3D)	Non GLP	Merck Research Laboratories West Point, PA USA	TT # [redacted] 1005	[Ref. 4.2.3.7.7: TT [redacted] 1005FIN]

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day[a])	GLP Compliance	Testing Facility	Study Number	CTD Location
Other Toxicity Studies (Other)								
7 Day Dose Range Finding Assay	Rat/Fischer 344: F344/NHsd	Oral (gavage)	7 days	0, 250, 500	Non GLP	[redacted] USA	TT # [redacted] 9027	[Ref. 4.2.3.7.7: TT [redacted] 9027FIN]
In Life Only: In vivo Mutation Assay at cII Locus	Rat (Big Blue® Transgenic F344)	Oral (gavage)	28 days	0, 50, 150, 500 Positive Control (20)	GLP o	[redacted] USA	TT # [redacted] 9047	[Ref. 4.2.3.7.7: TT [redacted] 9047FIN]
7 Day Tolerability	Monkey (rhesus)	Oral (gavage)	7 days	150, 300, 500	Non GLP	[redacted] USA	TT # [redacted] 7817	[Ref. 4.2.3.7.7: TT [redacted] 7817FIN]

Footnotes are presented on the following page.

Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: Molnupiravir

[redacted]; DMF N,N Dimethylformamide; GLP Good Laboratory Practice; [redacted]; No. Number; [redacted]; MTD Maximum tolerated dose; MK 4482 EIDD 2801 MOV; NA Not applicable; NHC N hydroxycytidine (EIDD 1931); NOAEL No observed adverse effect level; QD Once daily; Q3D Once every 3 days; SD Sprague Dawley; SN Study Number; TK Toxicokinetics.

Note: Two production intermediates for MOV (Drug Substance) were assessed for mutagenic potential according to the ICH M7(R1) guideline, and were negative in the microbial mutagenesis assays. The associated microbial mutagenesis (Ames test) study reports (TT # [redacted] 8030 and TT # [redacted] 8031) are located in Module 4.2.3.7.6.

a Doses are mg/kg/day unless otherwise specified. For the pivotal repeat dose toxicity studies, fertility, and definitive embryofetal and pre and postnatal developmental toxicity studies, the NOAEL (No Observed Adverse Effect Level), when applicable, is underlined/bolded.

b 28 day wild type CByB6F1 Tg(HRAS)2Jic mouse toxicity study (TT # [redacted] 9037): GLP with the exception of bioanalysis and TK evaluation of NHC. TK data for NHC are from the 7 day TK study in Wild Type CByB6F1 Tg(HRAS)2Jic mice (TT # [redacted] 9011).

c Merck Research Laboratories is a division of Merck, Sharp, & Dohme Corp. (MSD).

d 28 day dog toxicity study (TT # [redacted] 7815): Animals in the 50 mg/kg/day group received their last dose on Day 12 or 14, while animals in the 17 mg/kg/day group received their last dose on Day 21 (male) or 22 (female).

e In vitro microbial mutagenesis assay (TT # [redacted] 7810): GLP [redacted]

f In vitro micronucleus assay in TK 6 cells (TT # [redacted] 7806): GLP, [redacted]

g In vivo micronucleus assay (TT # [redacted] 7816): GLP, [redacted].

h In vivo Pig a assay (TT # [redacted] 7808): GLP, [redacted].

i Fertility studies (TT # [redacted] 9000 and TT # [redacted] 9012): GLP, [redacted].

j Preliminary (TT # [redacted] 7054) and definitive (TT # [redacted] 7000) embryo fetal developmental studies in rats: GLP, [redacted].

k Preliminary embryo fetal developmental study in rabbits (TT # [redacted] 7064): GLP, with the exception of bioanalytical sample results for NHC, [redacted]

l Definitive embryo fetal developmental studies in rabbits (TT # [redacted] 7010): GLP, [redacted].

m Pre and Postnatal Developmental Toxicity study (TT # [redacted] 9010): GLP, [redacted].

n Occupational safety studies (TT # [redacted] 7801, TT # [redacted] 7802, TT # [redacted] 7803): GLP [redacted].

o In Life Only: In vivo Mutation Assay at cII Locus (TT # [redacted] 9047): GLP [redacted].

Sec. 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies

Test Article: Molnupiravir

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Study Number	Location
NHC: 7 Day Dose Range Finding with TK	Mouse/Wild Type Crl:CD1® (ICR)	Oral (gavage)	0, 200, 500, 1000	No	TT #[redacted] 7850	[Ref. 4.2.3.2: TT[redacted]7850FIN]
28 Day (Dose Range Finding) Toxicity & TK (MOV only)	Mouse/CByB6F1 Tg(HRAS)2Jic	Oral (gavage)	0, 100, 300, 700, 2000	Yes	TT #[redacted] 9037	[Ref. 4.2.3.2: TT[redacted]9037FIN]
7 Day Dose Range Finding with TK	Rat/Hsd:SD	Oral (gavage)	0, 200, 700, 2000	No	TT #[redacted] 7825	[Ref. 4.2.3.2: TT[redacted]7825FIN]
28 Day Toxicity & TK with 14 Day Recovery Period	Rat/Hsd:SD	Oral (gavage)	0, 50, 150, 500	Yes	TT #[redacted] 7814	[Ref. 4.2.3.2: TT[redacted]7814FIN]
3 Month Toxicity and TK	Rat/Crl:CD(SD)	Oral (gavage)	0, 150 (males only), 200 (females only), 500, 1000	Yes	TT #[redacted] 1014	[Ref. 4.2.3.2: TT[redacted]1014FIN]
7 Day Dose Range Finding with TK	Dog (beagle)	Oral (gavage)	0, 100, 300, 1000	No	TT #[redacted] 7826	[Ref. 4.2.3.2: TT[redacted]7826FIN]
28 Day Toxicity & TK with 28 Day Recovery Period	Dog (beagle)	Oral (gavage)	0, 6, 17, 50	Yes	TT #[redacted] 7815	[Ref. 4.2.3.2: TT[redacted]7815FIN]
Fertility (Female)	Rat/Crl:CD(SD)	Oral (gavage)	0, 100, 250, 500	Yes	TT #[redacted] 9000	[Ref. 4.2.3.5.1: TT[redacted]9000FIN]
Fertility (Male)	Rat/Crl:CD(SD)	Oral (gavage)	0, 100, 250, 500	Yes	TT #[redacted] 9012	[Ref. 4.2.3.5.1: TT[redacted]9012FIN]
Preliminary Embryo fetal Developmental & TK	Rat/Crl:CD(SD)	Oral (gavage)	0, 100, 200, 500, 1000	Yes	TT #[redacted] 7054	[Ref. 4.2.3.5.2: TT[redacted]7054FIN]
Embryo fetal Developmental & TK (NHC only)	Rat/Crl:CD(SD)	Oral (gavage)	0, 100, 250, 500	Yes	TT #[redacted] 7000	[Ref. 4.2.3.5.2: TT[redacted]7000FIN]
Preliminary Embryo fetal Developmental & TK (MOV only)	Rabbit (Dutch Belted)	Oral (gavage)	0, 60, 200, 500, 1000	Yes	TT #[redacted] 7064	[Ref. 4.2.3.5.2: TT[redacted]7064FIN]

Sec. 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies

Test Article: Molnupiravir

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)	GLP Compliance	Study Number	Location
Embryo fetal Developmental & TK	Rabbit (Dutch Belted)	Oral (gavage)	0, 125, 400, 750	Yes	TT # [redacted] 7010	[Ref. 4.2.3.5.2: TT [redacted] 7010FIN]
Pre and Postnatal Development & TK	Rat/Crl:CD(SD)	Oral (gavage)	0, 100, 250, 500	Yes	TT # [redacted] 9010	[Ref. 4.2.3.5.3: TT [redacted] 9010FIN]
7 Day TK (NHC only)	Mouse/Wild Type CByB6F1 Tg(HRAS)2Jic	Oral (gavage)	100, 300, 700, 2000	Yes	TT # [redacted] 9011	[Ref. 4.2.3.7.7: TT [redacted] 9011FIN]
Exploratory 5 Day TK	Rat/ Crl:CD(SD); Rat/Fischer 344: F344/NHsd	Oral (gavage)	50, 150, 500,	No	TT # [redacted] 1015	[Ref. 4.2.3.7.7: TT [redacted] 1015FIN]
Exploratory 14 Day Tolerability & TK (Nonpregnant)	Rabbit (Dutch Belted)	Oral (gavage)	0, 3, 30, 300, 1000	No	TT # [redacted] 7043	[Ref. 4.2.3.7.7: TT [redacted] 7043FIN]
Exploratory 16 Day TK	Dog (beagle)	Oral (gavage)	6 (QD), 17 (Q3D)	No	TT # [redacted] 1005	[Ref. 4.2.3.7.7: TT [redacted] 1005FIN]
7 Day Dose Range Finding Assay	Rat/Fischer 344: F344/NHsd	Oral (gavage)	0, 250, 500	No	TT # [redacted] 9027	[Ref. 4.2.3.7.7: TT [redacted] 9027FIN]

GLP Good Laboratory Practice; GMP Good Manufacturing Practice; NHC N hydroxycytidine (EIDD 1931); QD Once daily; Q3D Once every 3 days; SD Sprague Dawley; SN Study Number; TK Toxicokinetics.

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: Molnupiravir

Daily Dose (mg/kg/day)	MOV AUC (0-24 hr or AUC last[a]) (µM*hr)							
	Mice		Rats		Dogs		Rabbits	Human[b]
	F	M	F	M	F	M	F	
6 (SD 1)						0.56 ([redacted] 7815)		
17 (SD 1)					0.68 ([redacted] 7815)	2.96 ([redacted] 7815)		
17 (Q3D) (SD1)						1.12 ([redacted] 1005)		
17 (Q3D) (SD16)						1.71 ([redacted] 1005)		
30 (SD 7)							0.155 ([redacted] 7043)	
50 (SD 1)					6.89 ([redacted] 7815)	5.34 ([redacted] 7815)		
50 (SD 5)				0.149(S D); 0.103(F344) ([redacted] 1015)				
60 (GD 15)							0.276 ([redacted] 7064)	
100 (SD 1)					6.7 ([redacted] 7826)			
100 (GD 15)			0.165 ([redacted] 7054)					
100 (LD 10)			0.190 ([redacted] 9010)					
150 (SD 1)				0.14 ([redacted] 7814)				

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: Molnupiravir

Daily Dose (mg/kg/day)	MOV AUC (0-24 hr or AUC last[a]) (µM*hr)							
	Mice		Rats		Dogs		Rabbits	Human[b]
	F	M	F	M	F	M	F	
150 (SD 5)				0.362 (S D); 0.475 (F344) ([redacted] 1015)				
150 (SW 2)				0.332 ([redacted] 1014)				
150 (SD 28)			0.31 ([redacted] 7814)	0.38 ([redacted] 7814)				
150 (SW 13)				0.557 ([redacted] 1014)				
200 (SW 2)			0.443 ([redacted] 1014)					
200 (GD 15)			0.272 ([redacted] 7054)					
200 (SW 13)			0.755 ([redacted] 1014)					
250 (SD 7)				0.228 ([redacted] 9027)				
250 (LD 10)			0.786 ([redacted] 9010)					
300 (SD 1)					26.7 ([redacted] 7826)			
300 (SD7)							0.547 ([redacted] 7043)	
300 (SD 28)	0.0928 ([redacted] 9037)	0.109 ([redacted] 9037)						

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: Molnupiravir

Daily Dose (mg/kg/day)	MOV AUC (0-24 hr or AUC last[a]) (µM*hr)							
	Mice		Rats		Dogs		Rabbits	Human[b]
	F	M	F	M	F	M	F	
500 (SD 1)			0.98 ([redacted] 7814)	0.61 ([redacted] 7814)				
500 (SD 5)				1.89 (S D); 2.00 (F344) ([redacted] 1015)				
500 (SD 7)				0.590 ([redacted] 9027)				
500 (SW 2)			1.07 ([redacted] 1014)	1.33 ([redacted] 1014)				
500 (SD 28)			1.17 ([redacted] 7814)	1.55 ([redacted] 7814)				
500 (SW 13)			2.63 ([redacted] 1014)	2.32 ([redacted] 1014)				
500 (GD 15)			1.31 ([redacted] 7054)				0.506 ([redacted] 7064)	
500 (LD 10)			1.79 ([redacted] 9010)					
700 (SD 28)		0.378 ([redacted] 9037)						
1000 (SD 1)					103 ([redacted] 7826)			
1000 (SD 7)							1.01 ([redacted] 7043)	

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: Molnupiravir

Daily Dose (mg/kg/day)	MOV AUC (0-24 hr or AUC last[a]) (µM*hr)							
	Mice		Rats		Dogs		Rabbits	Human[b]
	F	M	F	M	F	M	F	
1000 (SW 2)			3.29 ([redacted] 1014)	4.32 ([redacted] 1014)				
1000 (SW13)			4.43 ([redacted] 1014)	5.67 ([redacted] 1014)				
1000 (GD 15)			2.94 ([redacted] 7054)				0.702 ([redacted] 7064)	
2000 (SD 28)	1.38 ([redacted] 9037)							

F344 F344/NHsd; MOV Molnuupiravir MK 4482 (EIDD 2801); SD Study Day; S D Crl:CD(SD); SW Study Week

a: AUC_{last} for TT #[redacted] 7814 and TT #[redacted] 7815; AUC_{inf} for TT #[redacted] 7826 (Day 1)

b: Not applicable. MOV is generally undetectable in human plasma (LLOQ of 0.0152 µM).

TT #[redacted] 7826: Oral MTD/7 Day Dose Range Finding in Dogs
TT #[redacted] 7814: Oral 28 Day Toxicology and Toxicokinetics in Rats With a 14 Day Recovery
TT #[redacted] 7815: Oral MTD/7 Day Dose Range Finding in Dogs
TT #[redacted] 1014: Three Month Oral Toxicity and Toxicokinetic Study in Rats
TT #[redacted] 1015: Exploratory 5 Day Oral Toxicokinetic Study in Sprague Dawley and Fischer 344 Rats
TT #[redacted] 7043: Exploratory Oral 14 Day Tolerability and Toxicokinetic Study in Nonpregnant Rabbits
TT #[redacted] 7054: Preliminary Oral Embryo fetal Developmental Toxicity and Toxicokinetic Study in Rats
TT #[redacted] 7064: Preliminary Oral Embryo fetal Developmental Toxicity and Toxicokinetic Study in Rabbits
TT #[redacted] 9010: Oral Pre and Postnatal Development and Toxicokinetic Study in Rats
TT #[redacted] 9027: A 7 Day In Vivo Mammalian Dose Range Finder Assay in Fischer 344 Male Rats
TT #[redacted] 9037: A 28 Day Study in Wild Type CByB6F1 Tg(HRAS)2Jic Mice
TT #[redacted] 1005: Exploratory 16 Day Oral Toxicokinetic Study in Dogs

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: NHC

Daily Dose (mg/kg/day)	NHC AUC(0-24 hr or AUClast or AUCinf[a]) (µM*hr)									
	Mice		Rats		Dogs		Rabbits	Monkeys		Human[b]
	F	M	F	M	F	M	F	F	M	
3 (SD 7)							3.03 ([redacted] 7043)			
6 (SD 1)					7.48 ([redacted] 7815); 10.3 ([redacted] 1005)	6.91 ([redacted] 7815)				
6 (SD 16)					9.54 ([redacted] 1005)					
6 (SD 28)					9.41 ([redacted] 7815)	9.64 ([redacted] 7815)				
17 (SD 1)					30.86 ([redacted] 7815)	28.43 ([redacted] 7815)				
17(Q3D) (SD 1)						37.0 ([redacted] 1005)				
17(Q3D) (SD 16)						34.1 ([redacted] 1005)				
30 (SD 7)							30.7 ([redacted] 7043)			
50 (SD 1)			6.29 ([redacted] 7814)	22.22 ([redacted] 7814)	126.92 ([redacted] 7815)	110.72 ([redacted] 7815)				
50 (SD 5)				14.8 (S D); 6.50 (F344) ([redacted] 1015)						
50 (SD 28)			9.68 ([redacted] 7814)	20.91 ([redacted] 7814)						

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: NHC

Daily Dose (mg/kg/day)	NHC AUC(0-24 hr or AUClast or AUCinf[a]) (µM*hr)									
	Mice		Rats		Dogs		Rabbits	Monkeys		Human[b]
	F	M	F	M	F	M	F	F	M	
100 (SD1)					501 ([redacted] 7826)					
100 (SD 7)	24.8 ([redacted] 9011)	34.4 ([redacted] 9011)								
100 (SD 15)			14.9 ([redacted] 9000)	45.6 ([redacted] 9012)						
100 (GD 15)			22.5 ([redacted] 7054); 18.4 ([redacted] 7000)							
100 (LD 10)			9.12 ([redacted].9010)							
125 (GD 15)							111 ([redacted] 7010)			
150 (SD 1)			37.15 ([redacted] 7814)	108.40 ([redacted] 7814)				57.3 ([redacted] 7817)	42.1 ([redacted] 7817)	
150 (SD 5)				57.6 (S D); 29.8 (F344) ([redacted] 1015)						
150 (SD 7)								51.6 ([redacted] 7817)	41.1 ([redacted] 7817)	
150 (SW 2)				75.3 ([redacted] 1014)						
150 (SD 28)			42.43 ([redacted] 7814)	107.63 ([redacted] 7814)						

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: NHC

Daily Dose (mg/kg/day)	NHC AUC(0-24 hr or AUClast or AUCinf[a]) (µM*hr)									
	Mice		Rats		Dogs		Rabbits	Monkeys		Human[b]
	F	M	F	M	F	M	F	F	M	
150 (SW 13)					52.2 ([redacted] 1014)					
200 (SD 1)	21 ([redacted] 7850)		101 ([redacted] 7825)	205 ([redacted] 7825)						
200 (SD 7)	37 ([redacted] 7850)		96 ([redacted] 7825)	172 ([redacted] 7825)						
200 (SW 2)			108 ([redacted] 1014)							
200 (GD 15)			45.7 ([redacted] 7054)							
200 (SW 13)			67.6 ([redacted] 1014)							
250 (SD 7)				133 ([redacted] 9027)						
250 (SD 15)			61.4 ([redacted] 9000)	179 ([redacted] 9012)						
250 (GD 15)			58.3 ([redacted] 7000)							
250 (LD 10)			62.6 ([redacted] 9010)							
300 (SD 1)						1697 ([redacted] 7826)		141.7 ([redacted] 7817)	132.1 ([redacted] 7817)	
300 (SD7)	71.0 ([redacted] 9011)	82.5 ([redacted] 9011)					423 ([redacted] 7043)	229.9 ([redacted] 7817)	129.2 ([redacted] 7817)	
400 (GD 15)							490 ([redacted] 7010)			

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: NHC

Daily Dose (mg/kg/day)	NHC AUC(0-24 hr or AUClast or AUCinf[a]) (µM*hr)									
	Mice		Rats		Dogs		Rabbits	Monkeys		Human[b]
	F	M	F	M	F	M	F	F	M	
500 (SD 1)	59 ([redacted] 7850)		269.66 ([redacted] 7814)	432.07 ([redacted] 7814)				180.3 ([redacted] 7817)	338.1 ([redacted] 7817)	
500 (SD 5)				302 (S D); 159 (F344) ([redacted] 1015)						
500 (SD 7)	83 ([redacted] 7850)			233 ([redacted] 9027)				246.4 ([redacted] 7817)	302.4 ([redacted] 7817)	
500 (SW 2)			251 ([redacted] 1014)	362 ([redacted] 1014)						
500 (SD 15)			157 ([redacted] 9000)	463 ([redacted] 9012)						
500 (SD 28)			318.65 ([redacted] 7814)	590.23 ([redacted] 7814)						
500 (SW 13)			250 ([redacted] 1014)	408 ([redacted] 1014)						
500 (GD 15)			217 ([redacted] 7054)							
500 (LD 10)			122 ([redacted] 9010)							
700 (SD 1)			706 ([redacted] 7825)	960 ([redacted] 7825)						
700 (SD 7)	199 ([redacted] 9011)	272 ([redacted] 9011)	436 ([redacted] 7825)	1461 ([redacted] 7825)						
750 (GD 15)							1360 ([redacted] 7010)			

Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: NHC

Daily Dose (mg/kg/day)	NHC AUC(0-24 hr or AUClast or AUCinf[a]) (µM*hr)								
	Mice		Rats		Dogs		Rabbits	Monkeys	Human[b]
	F	M	F	M	F	M	F	F	M
1000 (SD 1)		128 ([redacted] 7850)				5011 ([redacted] 7826)			
1000 (SD 7)		143 ([redacted] 7850)					2210 ([redacted] 7043)		
1000 (SW 2)			660 ([redacted] 1014)	1280 ([redacted] 1014)					
1000 (SW13)			706 ([redacted] 1014)	1120 ([redacted] 1014)					
1000 (GD 15)			570 ([redacted] 7054)						
2000 (SD 1)			1271 ([redacted] 7825)	2180 ([redacted] 7825)					
2000 (SD 7)	1190 ([redacted] 9011)	1640 ([redacted] 9011)	4642 ([redacted] 7825)	6917 ([redacted] 7825)					

Footnotes are presented on the following page.

2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: NHC

F344 F344/NHsd; MOV Molnuupiravir MK 4482 (EIDD 2801); NHC N hydroxycytidine (EIDD 1931); SD Study Day; S D Crl:CD(SD); SW Study Week

a: AUC_{last} for TT #[redacted] 7814 and TT #[redacted] 7815; AUC_{inf} for TT #[redacted] 7825, TT #[redacted] 7826 (Day 1), TT #[redacted] 7817.

b: Human PK NHC value 75.6 µM*hr at 800 mg Q12H.

TT #[redacted] 7850: NHC Oral MTD/7 Day Dose Range Finding in Mice
TT #[redacted] 7825: Oral MTD/7 Day Dose Range Finding in Rats
TT #[redacted] 7826: Oral MTD/7 Day Dose Range Finding in Dogs
TT #[redacted] 7814: Oral 28 Day Toxicology and Toxicokinetics in Rats With a 14 Day Recovery
TT #[redacted] 7815: Oral MTD/7 Day Dose Range Finding in Dogs
TT #[redacted] 1014: Three Month Oral Toxicity and Toxicokinetic Study in Rats
TT #[redacted] 1015: Exploratory 5 Day Oral Toxicokinetic Study in Sprague Dawley and Fischer 344 Rats
TT #[redacted] 7043: Exploratory Oral 14 Day Tolerability and Toxicokinetic Study in Nonpregnant Rabbits
TT #[redacted] 7054: Preliminary Oral Embryo fetal Developmental Toxicity and Toxicokinetic Study in Rats
TT #[redacted] 7064: Preliminary Oral Embryo fetal Developmental Toxicity and Toxicokinetic Study in Rabbits
TT #[redacted] 9010: Oral Pre and Postnatal Development and Toxicokinetic Study in Rats
TT #[redacted] 9027: A 7 Day In Vivo Mammalian Dose Range Finder Assay in Fischer 344 Male Rats
TT #[redacted] 9037: A 28 Day Study in Wild Type CByB6F1 Tg(HRAS)2Jic Mice
TT #[redacted] 1005: Exploratory 16 Day Oral Toxicokinetic Study in Dogs
TT #[redacted] 7000: Oral Embryo fetal Developmental Toxicity and Toxicokinetic Study in Rats
TT #[redacted] 7010: Oral Embryo fetal Developmental Toxicity and Toxicokinetic Study in Rabbits
TT #[redacted] 9000: A Fertility Study by Oral Gavage Administration in Female Rats
TT #[redacted] 9011: A 7 Day Oral Gavage Toxicokinetic Study in Wild Type CByB6F1 Tg(HRAS)2Jic Mice
TT #[redacted] 9012: A Fertility Study by Oral Gavage Administration in Male Rats

Sec. 2.6.7.4 Toxicology: Drug Substance (GLP Studies Only)

Test Article: Molnupiravir

Batch No.	Purity (%)[2]	Specified Impurities[3] A[4]	B[5]	C[6]	Total Impurities (%)	Study Number	Type of Study
Proposed Specification[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT # [redacted] 7814	28 Day Toxicity & TK with 14 Day Recovery Period in Rats
						TT # [redacted] 7815	28 Day Toxicity & TK with 28 Day Recovery Period in Beagle Dogs
						TT # [redacted] 7806	In Vitro Micronucleus Induction Assay
						TT # [redacted] 7816	In Vivo Micronucleus Induction Assay
						TT # [redacted] 7808	Mammalian Peripheral Blood Erythrocyte Pig a Mutation Assay
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT # [redacted] 7810	Microbial Mutagenesis Assay
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT # [redacted] 9025	In Vivo Mutation Assay at cII Locus
						TT # [redacted] 9047	In Life Only: In Vivo Mutation Assay at cII Locus
						TT # [redacted] 7054	Preliminary Embryo fetal Developmental & TK in Rats
						TT # [redacted] 7000	Embryo fetal Developmental & TK in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT # [redacted] 9037	28 Day (Dose Range Finding) Toxicity & TK in Tg(HRAS) Mice
						TT # [redacted] 1014	3 Month Toxicity and TK in Rats (Batch used Weeks 1 9)
						TT # [redacted] 7064	Preliminary Embryo fetal Developmental & TK in Rabbits

Sec. 2.6.7.4 Toxicology: Drug Substance (GLP Studies Only)

Test Article: Molnupiravir

Batch No.	Purity (%)[2]	Specified Impurities[3] A[4]	B[5]	C[6]	Total Impurities (%)	Study Number	Type of Study
Proposed Specification[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT # [redacted] 7801	Bovine Corneal Opacity and Permeability (BCOP) Test
						TT # [redacted] 7802	MatTek EpiDerm™ MTT Viability Assay
						TT # [redacted] 7803	Local Lymph Node Assay in Mice (LLNA)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT # [redacted] 1014	3 Month Toxicity and TK in Rats *(Batch used Weeks 9 14)*
						TT # [redacted] 9000	Fertility Study in Female Rats
						TT # [redacted] 7010	Embryo fetal Developmental & TK in Rabbits
						TT # [redacted] 9011	7 Day TK in Tg(HRAS) Mice
						TT # [redacted] 9010	Pre and Postnatal Development & TK in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT# [redacted] 9012	Fertility Study in Male Rats

[redacted];

1 See Quality section for complete specification. See Section S.4.1
2 Purity: [redacted]
3 Specified impurities [redacted]
4 N hydroxycytidine (NHC, EIDD 1931, active metabolite of molnupiravir)
5 [redacted] ([redacted])
6 Individual unspecified impurity. [redacted]

Sec. 2.6.7.5 Single-Dose Toxicity

Single dose toxicity was assessed in Phase A of the single-dose MTD/7-day dose-range finding studies in mice (TT #[redacted]-7850), rats (TT #[redacted]-7825) and dogs (TT #[redacted]-7826) discussed under Repeat-Dose Toxicity Non-Pivotal Studies [Sec. 2.6.7.6].

MTD maximum tolerated dose

Sec. 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies

Test Article: Molnupiravir

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Mouse: Crl:CD1® (ICR)	Oral (gavage) in 240 mM citrate buffer in distilled water	1 day (MTD)	NHC: 500, 1000, 1500, 2000	3	NA	Decreases in food consumption in both sexes at ≥1500 mg/kg, body weight loss in females at ≥1500 mg/kg, and decreased body weight gain in males at 2000 mg/kg during the first few days post treatment.	TT #[redacted] 7850 (Phase A) [Ref. 4.2.3.2: TT[redacted]7 850FIN]
		7 days	NHC: 0, 200, 500, 1000	10	NA	No test article related findings.	TT #[redacted] 7850 (Phase B)
Rat/Hsd:SD	Oral (gavage) in 1% Methylcellulose (400 cps) in deionized water	1 day (MTD)	500, 1000, 1500,2000	2	NA	2000 mg/kg: Mean body weight loss (2.0 to 3.6 g) for males and females during the first few days post treatment, which correlated with 30% decreases in food consumption.	TT #[redacted] 7825 (Phase A) [Ref. 4.2.3.2: TT[redacted]7 825FIN]
		7 days	0, 200, 700, 2000	5	NA	≤700 mg/kg/day: No test article related findings. 2000 mg/kg/day: Clinical signs of toxicity (soiling, piloerection, unkempt appearance, and evidence of dehydration) and significantly decreased body weights in males with changes in hematology parameters, including decreased RET count, white blood cell, and absolute lymphocyte counts. Males had clinical chemistry changes that included slightly increased liver enzymes (ALT and AST). Females showed only mild elevations of ALT, calcium, glucose, and inorganic phosphorus. The improved tolerability in females compared with males at 2000 mg/kg/day is likely attributable to 1.4 to 3.4 fold lower exposures in females compared with males.	TT #[redacted] 7825 (Phase B)

Sec. 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies (Continued)

Test Article: Molnupiravir

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Dog (beagle)	Oral (gavage) in 1% Methylcellulose (400 cps) in deionized water	Rising dose	300, 500, 1000, 2000	1	NA	Clinical signs limited to minimal, transient GI effects, including emesis and soft feces at ≥300 mg/kg. All Phase A animals lost weight by Day 3, which corresponded to decreases in food consumption.	TT #[redacted] 7826 (Phase A) [Ref. 4.2.3.2: TT[redacted]7826FIN]
		Up to 7 days	0, 100, 300, 1000	2	NA	Doses of 300 and 1000 mg/kg/day exceeded the MTD due to early termination of the dose groups following, clinical signs of poor and deteriorating physical condition and notable body weight losses. MOV was tolerated in dogs administered 100 mg/kg/day for up to 7 days, with body weight loss noted form Day 5. Specifics are below. • Mortality: 1000 mg/kg/day 1 male euthanized on Day 4 due to marked clinical signs of toxicity (recumbency, pale mucous membranes, ulceration in the oral cavity, black tarry stool, tachycardia, and other indicators of shock). Surviving high dose dogs also necropsied on Day 4. Animals at 300 mg/kg/day were necropsied on Day 7 (rather than Day 8) due to clinical signs of poor and deteriorating physical condition. • Antemortem: Decreased activity, emesis, diarrhea, and partial eyelid closure) in males at ≥300 mg/kg/day and in all females at ≥100 mg/kg/day. Progressive, dose responsive decreases in mean body weight by Day 4 in dogs administered ≥300 mg/kg/day and by Day 5 in the 100 mg/kg/day groups, with correlating decreases in food consumption. • Clinical Pathology: ≥300 mg/kg/day decreases in absolute lymphocyte counts, increases in AST (30 fold), increased ALP, ALT (up to 5 fold), total cholesterol, and triglycerides, with decreased potassium, chloride, and calcium. • Postmortem:≥100 mg/kg/day: Macroscopic observations primarily associated with the GI tract (including the mouth, esophagus, and large and small intestines) included red and/or darkened foci, discolored mucosa (dark, red, and/or green), and thickened mucosa. ≥300 mg/kg/day: Dose responsive, organ weight changes noted most often in reproductive organs and liver, spleen, and thymus.	TT #[redacted] 7826 (Phase B)

Sec. 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies (Continued)

Test Article: Molnupiravir

ALT alanine aminotransferase; ALP alkaline phosphatase; AST aspartate aminotransferase; GI Gastrointestinal; MOV molnupiravir MK 4482 (EIDD 2801); MTD Maximum Tolerated Dose; NA Not Applicable; NHC N hydroxycytidine (EIDD 1931); NOAEL no observed adverse effect level; RET Reticulocyte Count; SD Sprague Dawley

Sec. 2.6.7.7A Repeat-Dose Toxicity: Report Title: A 28-Day Study in Wild Type CByB6F1 Tg(HRAS)2Jic Mice (TT #[redacted]-9037)

Test Article: Molnupiravir

Species/Strain: Mouse/Wild Type CByB6F1 Tg(HRAS)2Jic
Initial Age: ~10 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 28 days
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle/Formulation: 1% Methylcellulose (400 cps) in deionized water

Study Number: TT #[redacted]-9037
Location in CTD: [Ref. 4.2.3.2: TT[redacted]9037FIN]
GLP Compliance: Yes[a]

Special Features: None
No-Observed-Adverse-Effect Level: 300 mg/kg/day

Toxicokinetics – Study Day 28 — **MOV**

Daily Dose (mg/kg)	0 (Control)		100		300		700		2000	
Number of Animals	F:3[c]	M:3[c]	F:18	M:18	F:18	M:18	F:18	M:18	F:18	M:18
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	NA	NC[d]	NC[d]	0.0928	0.109	NC[e]	0.378	1.38	NC[e]
C_{max} (μM)	NA	NA	0.0442	0.0331	0.132	0.187	0.225	0.409	0.833	1.42
T_{max} (hr)	NA	NA	0.500	0.500	0.500	0.500	0.5	0.500	1.00	0.5

Toxicokinetics – Study Day 7[b] — **NHC**

TK data for NHC are from the 7 day TK study in Wild Type CByB6F1 Tg(HRAS)2Jic mice (TT #[redacted] 9011)

Daily Dose (mg/kg)	0 (Control)		100		300		700		2000	
Number of Animals	F:0	M:0	F:18	M:18	F:18	M:18	F:18	M:18	F:18	M:18
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	NA	24.8	34.4	71.0	82.5	199	272	1,190	1,640
C_{max} (μM)	NA	NA	22.8	24.7	78.1	71.8	205	223	844	1,080
T_{max} (hr)	NA	NA	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500

Sec. 2.6.7.7A Repeat-Dose Toxicity **Study No.:** TT #[redacted]-9037 [Ref. 4.2.3.2: TT[redacted]9037FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		100		300		700		2000	
Number of Animals (Main Study)	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Noteworthy Findings										
Mortality (No. of Animals)	0	0	0	0	0	0	0	0	0	0
Body Weight (Day 29)[f]	25.78 g	32.13 g	+1.3	-2.1	+0.9	-1.7	-2.3	-5.5	-4.2	-6.8
Body Weight Change (%)[g]	3.38 g	3.0 g	+8.3	[-28]	+6.8	[-24]	[-30]	[-56]	[-30]	[-77]
Food Consumption	-	-	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-	-	-
Serum Biochemistry	-	-	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-	-	-
Histopathology	-	-	NE	NE	NE	NE	NE	NE	-	-

No noteworthy findings; [ ] Test article related change based on incidence and/or severity; MOV molnupiravir MK 4482 (EIDD 2801); NA Not applicable; NE Group not examined; NHC N hydroxycytidine (EIDD 1931).

a GLP with the exception of bioanalysis and TK evaluation of NHC in TT #[redacted] 9037.

b TK data for NHC are from the 7 day TK study in Wild Type CByB6F1 Tg(HRAS)2Jic mice (TT #[redacted] 9011).

c MOV concentrations in plasma from all control group animals were below the LLOQ.

d Not calculated due to insufficient data; MOV concentrations were <LLQ of the bioanalytical assay after 1 hour postdose.

e Not calculated due to concentration values that had no result.

f At end of dosing period (Day 29). For controls, group means are shown. For dose groups, percent differences from controls are shown.

g The difference in body weight (g) between Day 1 and Day 29. For controls, group means are shown. For dose groups, percent difference from controls is shown.

Sec. 2.6.7.7B Repeat-Dose Toxicity: Report Title: 28-Day GLP Toxicity and Toxicokinetic Study of EIDD-2801 in Sprague Dawley Rats with a 14-Day Recovery Period (TT #[redacted]-7814)

Test Article: Molnupiravir

Species/Strain: Rat/Hsd:SD
Initial Age: 8 to 9 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 28
Duration of Postdose: 14 days
Method of Administration: Oral (gavage)
Vehicle/Formulation: 1% Methylcellulose (400 cps) in deionized water

Study Number: TT #[redacted]-7814
Location in CTD:
[Ref. 4.2.3.2: TT[redacted]7814FIN]
GLP Compliance: Yes

Special Features: 5 rats/sex/group assigned to 14-day recovery phase
No-Observed-Adverse-Effect Level: ≥500 mg/kg/day

MOV (Day 1)

Daily Dose (mg/kg)	0 (Control)[a]		50		150		500	
Number of Animals	F:3	M:3	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 1								
AUC_{last} (μM•hr)	N/A	N/A	ND	ND	ND	0.14	0.98	0.61
C_{max} (μM)	N/A	N/A	BLQ	BLQ	BLQ	0.13	0.92	0.60
$t_{1/2}$ (hr)	N/A	N/A	ND	ND	ND	ND	1.26	0.582

MOV (Day 28)

Daily Dose (mg/kg)	0 (Control)[b]		50		150		500	
Number of Animals	F:3	M:3	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 28			ND	ND				
AUC_{last} (μM•hr)	N/A	N/A	BLQ	BLQ	0.31	0.38	1.17	1.55
C_{max} (μM)	N/A	N/A	ND	ND	0.21	0.20	1.01	1.14
$t_{1/2}$ (hr)	N/A	N/A	ND	ND	ND	ND	ND	2.15

Sec. 2.6.7.7B Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7814 [Ref. 4.2.3.2: TT[redacted]7814FIN] (Continued)

			NHC (Day 1)					
Daily Dose (mg/kg)	0 (Control)[a]		50		150		500	
Number of Animals	F:3	M:3	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 1								
AUC_{last} (μM•hr)	N/A	N/A	6.29	22.22	37.15	108.40	269.66	432.07
C_{max} (μM)	N/A	N/A	3.76	10.96	22.64	44.36	150.84	175.53
$t_{1/2}$ (hr)	N/A	N/A	2.04	2.22	1.69	2.58	3.98	6.11

			NHC (Day 28)					
Daily Dose (mg/kg)	0 (Control)[a]		50		150		500	
Number of Animals	F:3	M:3	F:9	M:9	F:9	M:9	F:9	M:9
Toxicokinetics – Study Day 28								
AUC_{last} (μM•hr)	N/A	N/A	9.68	20.91	42.43	107.63	318.65	590.23
C_{max} (μM)	N/A	N/A	6.06	10.49	24.03	52.08	181.70	213.33
$t_{1/2}$ (hr)	N/A	N/A	1.65	2.10	1.44	2.45	3.36	3.36

Sec. 2.6.7.7B Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7814 [Ref. 4.2.3.2: TT[redacted]7814FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		50		150		500	
Number of Animals - Main	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Number of Animals – Recovery	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Noteworthy Findings								
Mortality (No. of Animals) (Main & Recovery)	0	0	0	0	0	0	0	0
Body Weight (Main & Recovery)	-	-	-	-	-	-	-	-
Food Consumption Main & Recovery)	-	-	-	-	-	-	-	-
Clinical Observations (Main & Recovery)	-	-	-	-	-	-	-	-
Ophthalmoscopy (Main & Recovery)	-	-	-	-	-	-	-	-

Sec. 2.6.7.7B Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7814 [Ref. 4.2.3.2: TT[redacted]7814FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		50		150		500	
Number of Animals - Main	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Number of Animals – Recovery	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Noteworthy Findings (continued)								
Hematology (Main & Recovery)	-	-	-	-	-	-	-	-
Coagulation (Main & Recovery)	-	-	-	-	-	-	-	-
Serum Biochemistry (Main & Recovery)	-	-	-	-	-	-	-	-
Urinalysis (Main & Recovery)	-	-	-	-	-	-	-	-
Organ Weights (Main)								
Liver[b,c]	369.702	549.423	+2.164	+5.607	+2.053	+2.244	[+11.655]	[+16.571]*
Organ Weights (Recovery)	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology (Main & Recovery)	-	-	NE	NE	NE	NE	-	-

No noteworthy findings; [ ] Test article related change based on incidence and/or severity;
BLQ Below the limit of quantification; MOV molnupiravir MK 4482 (EIDD 2801); NA Not applicable; ND Not determined; NE Group not examined; NHC N hydroxycytidine (EIDD 1931).
* $p < 0.05$; ** $p < 0.01$ (ANOVA or ANOVA DUNNETT)

a Plasma concentrations from all control group animals were below the LLOQ on Day 1 and Day 28.
b Control values are the mean organ weight as a percent of brain weight; treatment group values are the mean percent change from concurrent controls of organ weight relative to brain weight.
c The increase in liver weights at 500 mg/kg/day had no histopathologic correlate and were considered non adverse.

Sec. 2.6.7.7C Repeat-Dose Toxicity: Report Title: Three-Month Oral Toxicity Study in Rats (TT #[redacted]-1014)

Test Article: Molnupiravir

Species/Strain: Rat/Crl:CD(SD)
Initial Age: 5 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 91 or 92 days
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle/Formulation: 1% Methylcellulose in deionized water

Study Number: TT #[redacted]-1014
Location in CTD:
[Ref. 4.2.3.2: TT[redacted]1014FIN]
GLP Compliance: Yes

Special Features: None
No-Observed-Adverse-Effect Level: 150 mg/kg/day (males), 500 mg/kg/day (females)

MOV (Week 2)

Daily Dose (mg/kg)	0 (Control)[a]		150		200		500		1000	
Number of Animals	F:9	M:9	F:0	M:9	F:9	M:0	F:9	M:9	F:9	M:9
Toxicokinetics (Week 2)										
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	NA	NA	0.332	0.443	NA	1.07	1.33	3.29	4.32
C_{max} (μM)	NA	NA	NA	0.171	0.270	NA	0.569	0.487	1.50	1.43
T_{max} (hr)	NA	NA	NA	0.500	0.500	NA	0.500	0.500	0.500	0.500

MOV (Week 13)

Daily Dose (mg/kg)	0 (Control)[b]		150		200		500		1000	
Number of Animals	F:9	M:9	F:0	M:9	F:9	M:0	F:9	M:9	F:9	M:9
Toxicokinetics (Week 13)										
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	NA	NA	0.557	0.755	NA	2.63	2.32	4.43	5.67
C_{max} (μM)	NA	NA	NA	0.402	0.605	NA	1.29	0.966	2.15	1.79
T_{max} (hr)	NA	NA	NA	0.500	0.500	NA	0.500	0.500	0.500	2.00

Sec. 2.6.7.7C Repeat-Dose Toxicity **Study No.:** TT #[redacted]-1014 [Ref. 4.2.3.2: TT[redacted]1014FIN] (Continued)

NHC (Week 2)

Daily Dose (mg/kg)	0 (Control)[a]		150		200		500		1000	
Number of Animals	F:9	M:9	F:0	M:9	F:9	M:0	F:9	M:9	F:9	M:9
Toxicokinetics (Week 2)										
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	NA	NA	75.3	108	NA	251	362	660	1280
C_{max} (μM)	NA	NA	NA	27.5	63.4	NA	97.5	140	265	260
T_{max} (hr)	NA	NA	NA	1.00	0.500	NA	1.00	1.00	1.00	1.00

NHC (Week 13)

Daily Dose (mg/kg)	0 (Control)[a]		150		200		500		1000	
Number of Animals	F:9	M:9	F:0	M:9	F:9	M:0	F:9	M:9	F:9	M:9
Toxicokinetics (Week 13)										
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	NA	NA	52.2	67.6	NA	250	408	706	1120
C_{max} (μM)	NA	NA	NA	15.6	57.2	NA	161	148	301	279
T_{max} (hr)	NA	NA	NA	2.00	0.500	NA	0.500	1.00	0.500	1.00

Sec. 2.6.7.7C Repeat-Dose Toxicity **Study No.:** TT #[redacted]-1014 [Ref. 4.2.3.2: TT[redacted]1014FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		150		200		500		1000	
Number of Animals	F:10	M:10	F:0	M:10	F:10	M:0	F:10	M:10	F:10	M:10
Noteworthy Findings										
Mortality (No. of Animals)	0	0	0	0	0	0	0	0	0	0
Body Weight (Week 13) (%)[c]	312.8	598.7	NA	[-9]	+0.7	NA	-5.6	[-18.7]	-4.9	[-41.3]
Body Weight Change (%)[d]	180.7	460.6	NA	[-13]	+0.7	NA	[-8]	[-25]	[-9]	[-55]
Food Consumption Decreased (very slight to slight over course of study)	NA	NA	NA	[D]	-	NA	[D]	[D]	[D]	[D]
Clinical Observations	-	-	NA	-	-	NA	-	-	-	-
Ophthalmoscopy	-	-	NA	-	-	NA	-	-	-	-
Hematology	-	-	NA	-	-	NA	-	-	-	-
Serum Biochemistry	-	-	NA	-	-	NA	-	-	-	-
Urinalysis	-	-	NA	-	-	NA	-	-	-	-
Organ Weights	-	-	NA	-	-	NA	-	-	-	-
Gross Pathology	-	-	NA	-	-	NA	-	-	-	-

Sec. 2.6.7.7C Repeat-Dose Toxicity **Study No.:** TT #[redacted]-1014 [Ref. 4.2.3.2: TT[redacted]1014FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		150		200		500		1000	
Number of Animals	F:10	M:10	F:0	M:10	F:10	M:0	F:10	M:10	F:10	M:10
Noteworthy Findings (continued)										
Histomorphology (Incidence)										
Bone, Femur					NE					
Physis, increased thickness	0/10	0/10	NA	0/10		NA	0/10	0/10	0/10	10/10
Epiphysis, cartilage, increased thickness	0/10	0/10	NA	0/10		NA	0/10	10/10	10/10	10/10
Trachea					NE		NE			
Cartilage, chondrocyte, cytoplasmic alteration, eosinophilic	0/10	0/10	NA	0/10		NA		6/10	0/10	10/10

No noteworthy findings; [ ] Test article related change based on incidence and/or severity; D Decreased; MOV molnupiravir MK 4482 (EIDD 2801); NA Not applicable; NE Group not examined; NHC N hydroxycytidine (EIDD 1931)

a Plasma concentrations from all control group animals were below the LLOQ at Week 2 and Week 13.

b MOV concentrations in plasma from all control group animals were above the lower limit of quantitation of the bioanalytical method in Study Week 13. These values were approximately 5.6% or less of the mean C_{max} value of the low dose group.

c At end of dosing period (Week 13). For controls, group means are shown. For dose groups, percent differences from controls are shown.

d The difference in body weight (g) between pretest and Week 13. For controls, group means are shown. For dose groups, percent difference from controls is shown.

Sec. 2.6.7.7D Repeat-Dose Toxicity: Report Title: 28-Day Oral GLP Toxicity and Toxicokinetic Study of EIDD-2801 in Beagle Dogs with a 28-Day Recovery Period (TT #[redacted]-7815)

Test Article: Molnupiravir

Species/Strain: Dog (beagle)
Initial Age: 6 to 7 months
Date of First Dose: [redacted]
Dose Volume: 2 mL/kg

Duration of Dosing: Up to 28 days*
Duration of Postdose: See description below*
Method of Administration: Oral (gavage)
Vehicle/Formulation: 1% Methylcellulose (400 cps) in deionized water

Study Number: TT #[redacted]-7815
Location in CTD:
[Ref. 4.2.3.2: TT[redacted]7815FIN]
GLP Compliance: Yes

***Duration of Dosing & Postdose:** 3 dogs/sex/group were assigned to terminal sacrifice groups and 2 dogs/sex/group were assigned to recovery groups. Dogs dosed with 50 mg/kg/day received 12 or 14 doses; dogs dosed with 17 mg/kg/day received 21 doses (until Study Day 21 or 22 – staggered start). Recovery necropsy for dogs dosed with 50 mg/kg/day = Study Day 23/24; other recovery animals were necropsied at the end of the 28-day recovery phase (Study Day 57).

Dose (mg/kg/day)	No. of Doses Received	Treatment Phase Necropsy (Study Day)	Recovery Phase Necropsy (Study Day)
0	28	Day 29	Day 57 (28 day recovery period)
6	28	Day 29	Day 57 (28 day recovery period)
17	21	Day 23/24	Day 57 (35 day recovery period)
50	12 or 14	Day 16/17	Day 23/24 (8 to 11 day recovery period)

Special Features: None

No-Observed-Adverse-Effect Level: 6 mg/kg/day

	MOV (Day 1)							
Daily Dose (mg/kg)	0 (Control)[a]		6		17		50	
Number of Animals	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Toxicokinetics –Day 1								
AUC_{last} (μM•hr)	N/A	N/A	ND	0.56	0.68	2.96	6.89	5.34
C_{max} (μM)	N/A	N/A	0.47	0.61	2.02	2.88	7.83	8.38
$t_{1/2}$ (hr)	N/A	N/A	ND	1.18	ND	ND	0.853	1.87

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

MOV (Day 28)

Daily Dose (mg/kg)	0 (Control)[a]		6		17		50	
Number of Animals	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Toxicokinetics –Day 28								
AUC_{last} (µM•hr)	N/A	N/A	ND	ND	Euth	Euth	Euth	Euth
C_{max} (µM)	N/A	N/A	0.46	0.38	Euth	Euth	Euth	Euth
$t_{1/2}$ (hr)	N/A	N/A	ND	ND	Euth	Euth	Euth	Euth

NHC (Day 1)

Daily Dose (mg/kg)	0 (Control)[a]		6		17		50	
Number of Animals	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Toxicokinetics –Day 1								
AUC_{last} (µM•hr)	N/A	N/A	7.48	6.91	30.86	28.43	126.92	110.72
C_{max} (µM)	N/A	N/A	5.83	4.82	17.67	15.43	50.15	54.01
$t_{1/2}$ (hr)	N/A	N/A	2.51	1.08	9.09	7.74	6.26	8.38

NHC (Day 28)

Daily Dose (mg/kg)	0 (Control)[a]		6		17		50	
Number of Animals	F:5	M:5	F:5	M:5	F:5	M:5	F:5	M:5
Toxicokinetics –Day 28								
AUC_{last} (µM•hr)	N/A	N/A	9.41	9.64	Euth	Euth	Euth	Euth
C_{max} (µM)	N/A	N/A	6.29	6.29	Euth	Euth	Euth	Euth
$t_{1/2}$ (hr)	N/A	N/A	4.26	9.05	Euth	Euth	Euth	Euth

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings								
Mortality (No. of Animals) - Main[b]	0	0	0	0	[3]	[3]	[3]	[3]
Mortality (No. of Animals) - Recovery[b]	0	0	0	0	0	0	[2]	[2]
Body Weight – Main[c]	-	-	-	-	-	-	[D] (12% to 17% below pretest)	[D] (5% to 14% below pretest)
Body Weight (kg) - Recovery	-	-	-	-	-	-	-	-
Food Consumption – Main	-	-	-	-	-	-	[D]	[D]
Food Consumption – Recovery	-	-	-	-	-	-	-	-

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Clinical Observations - Main								
Feces, discolored					[1]		[1]	
Decreased activity					[1]			[2]
Oral mucosa, discolored								[2]
Clinical Observations – Recovery								
Oral mucosa, discolored								[1]
Ophthalmoscopy (Main)	-	-	-	-	NE	NE	NE	NE
Ophthalmoscopy (Recovery)	-	-	-	-	-	-	NE	NE
Electrocardiography (Main)	-	-	-	-	NE	NE	NE	NE
Electrocardiography (Recovery)	-	-	-	-	-	-	NE	NE

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology[d]								
Eosinophils (10^3 cells/µL) - Main								
Pretest (Day -22)	0.20	0.23	0.21	0.15	0.32	0.18	0.13	0.16
Day 7	0.23	0.24	0.19	0.16	0.14	0.17	0.08	0.12
Day 14	0.20	0.22	0.17	0.14	0.10	0.08	[0.04]	[0.05]
Day 16, 17 or 21	0.18	0.25	0.12	0.12*	[0.03]	[0.03**]	[0.04]	[0.05]
Day 23 or 24	0.21	0.24	0.14	0.11*	[0.02]	[0.02**]	NA	NA
Eosinophils (10^3 cells/µL) – Recovery								
Day 21	NA	NA	NA	NA	NA	NA	[0.07]	[0.02]
Day 23 or 24	NA	NA	NA	NA	NA	NA	[0.05]	[0.03]
Day 28	NA	NA	NA	NA	[0.01]	[0.07]	NA	NA
Day 34 or 35	0.15	0.28	0.11	0.10	[0.05]	0.16	NA	NA
Day 41 or 42	0.11	0.11	0.15	0.16	[0.07]	0.21	NA	NA
Day 48 or49	0.12	0.20	0.15	0.24	0.14	0.18	NA	NA
Day 55 or 56	0.11	0.17	0.19	0.25	0.25	0.21	NA	NA
Day 57	0.10	0.16	0.28	0.23	0.28	0.22	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Hematocrit (%) - Main								
Pretest	42.7	42.4	44.9	41.8	42.6	43.7	43.0	41.4
Day 7	46.0	48.1	46.7	46.4	44.1	42.7**	42.9	41.1
Day 14	46.1	47.8	46.9	46.6	40.2	40.6**	43.0	41.0
Day 16, 17 or 21	44.4	46.0	46.6	43.5	[36.1]	[35.3**]	43.3	41.9
Day 23 or 24	45.6	45.0	44.3	42.1	[34.6]	[38.2**]	NA	NA
Hematocrit (%) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	[38.3]	[36.0]
Day 23 or 24	NA	NA	NA	NA	NA	NA	[33.3]	[33.3]
Day 28	NA	NA	NA	NA	[34.8]	40.4	NA	NA
Day 34 or 35	42.2	48.4	46.3	47.0	[37.9]	39.8	NA	NA
Day 41 or 42	45.0	51.9	50.7	51.3	44.0	44.9	NA	NA
Day 48 or 49	48.0	51.4	48.6	53.0	47.4	44.6	NA	NA
Day 55 or 56	44.7	50.3	48.9	52.2	46.2	45.2	NA	NA
Day 57	42.6	49.0	44.9	48.0	44.2	40.9	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Hemoglobin (g/dL)- Main								
Pretest	14.4	14.2	15.1	13.7	14.3	14.5	14.3	13.8
Day 7	15.2	16.0	15.5	15.3	14.7	14.4**	14.3	13.8
Day 14	15.4	15.9	15.8	15.4	13.7	13.7**	14.6	13.6
Day 16, 17 or 21	14.9	15.6	15.5	14.6	12.3	12.0**	14.5	14.0
Day 23 or 24	15.4	15.3	15.0	14.2	[11.7]	12.9**	NA	NA
Hemoglobin (g/dL)- Recovery								
Day 21	NA	NA	NA	NA	NA	NA	13.2	12.1
Day 23 or 24	NA	NA	NA	NA	NA	NA	11.3	11.3
Day 28	NA	NA	NA	NA	[11.8]	13.6	NA	NA
Day 34 or 35	14.5	16.4	15.6	15.6	12.6	13.2	NA	NA
Day 41 or 42	15.4	17.6	17.0	17.0	14.5	14.9	NA	NA
Day 48 or 49	16.4	17.6	16.2	17.8	15.5	15.0	NA	NA
Day 55 or 56	15.6	17.4	16.8	17.6	15.4	15.4	NA	NA
Day 57	15.1	16.8	15.4	16.3	15.0	14.0	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Lymphocytes (10^3 cells/µL) - Main								
Pretest (Day -22)	2.65	2.83	2.67	2.27	2.99	3.23	2.53	3.11
Day 7	3.50	3.28	3.29	2.68	[2.71]	[2.57]	[1.69]	[2.35]
Day 14	3.16	2.91	2.83	2.53	[2.13]	[2.25]	[1.44]	[1.86]
Day 16, 17 or 21	2.69	3.07	2.80	2.38	[2.20]	[1.94]	[1.40]	[1.99]
Day 23 or 24	2.80	2.65	2.57	1.71	[2.07]	[2.17]	NA	NA
Lymphocytes (10^3 cells/µL) – Recovery								
Day 21	NA	NA	NA	NA	NA	NA	3.03	2.30
Day 23 or 24	NA	NA	NA	NA	NA	NA	2.28	2.41
Day 28	NA	NA	NA	NA	3.16	2.41	NA	NA
Day 34 or 35	3.43	3.18	3.54	2.82	3.52	2.52	NA	NA
Day 41 or 42	3.70	3.84	3.51	3.01	3.41	2.74	NA	NA
Day 48 or49	3.44	3.03	3.52	2.81	3.66	2.54	NA	NA
Day 55 or 56	3.82	3.47	3.94	3.20	4.04	2.72	NA	NA
Day 57	2.55	2.43	2.82	2.16	3.04	2.11	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Monocytes (10^3 cells/µL) - Main								
Pretest	0.52	0.92	0.56	1.09	0.45	0.84	0.49	1.06
Day 7	0.70	0.61	0.52	0.53	0.55	0.40**	0.58	0.53
Day 14	0.52	0.65	0.39	0.56	0.18	0.16**	0.29	0.24
Day 16, 17 or 21	0.53	0.62	0.33**	0.51	[0.05]	[0.07**]	0.23	0.23
Day 23 or 24	0.45	0.66	0.28**	0.45**	[0.09]	0.17**	NA	NA
Monocytes (10^3 cells/µL) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	0.64	0.41
Day 23 or 24	NA	NA	NA	NA	NA	NA	0.64	0.55
Day 28	NA	NA	NA	NA	0.34	0.47	NA	NA
Day 34 or 35	0.48	0.74	0.50	0.70	0.55	0.69	NA	NA
Day 41 or 42	0.44	0.52	0.52	0.54	0.69	0.74	NA	NA
Day 48 or 49	0.51	0.56	0.36	0.59	0.67	0.44	NA	NA
Day 55 or 56	0.38	0.68	0.50	0.54	0.65	0.42	NA	NA
Day 57	0.40	0.58	0.41	0.50	0.42	0.40	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Neutrophils (10^3 cells/µL) - Main								
Pretest	6.77	6.45	6.18	6.04	4.89	6.90	4.03	7.88
Day 7	7.18	4.64	5.51*	4.47	6.92	[3.64]	7.39	6.57
Day 14	6.00	5.20	4.93*	4.94	5.08	[4.07]	6.70	5.16
Day 16, 17 or 21	6.71	6.02	4.46*	5.00	[0.88]	[0.84**]	4.73	[3.00]
Day 23 or 24	6.05	6.17	4.64*	4.49	[1.23]	[1.60**]	NA	NA
Neutrophils (10^3 cells/µL) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	3.46	3.08
Day 23 or 24	NA	NA	NA	NA	NA	NA	3.63	2.96
Day 28	NA	NA	NA	NA	2.44	6.35	NA	NA
Day 34 or 35	7.14	7.12	5.62	5.66	5.41	6.21	NA	NA
Day 41 or 42	6.46	6.60	6.10	5.91	5.54	6.10	NA	NA
Day 48 or 49	6.45	5.84	4.64	5.40	6.27	4.76	NA	NA
Day 55 or 56	6.62	6.44	5.62	5.31	7.70	4.53	NA	NA
Day 57	5.88	5.29	5.29	4.44	4.81	3.99	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Platelet Counts (10^3 cells/µL) - Main								
Pretest	306	279	313	286	240	287	327	270
Day 7	257	230	261	252	242	215	208	201
Day 14	286	213	230*	228	[100]	[82**]	[53]	[37]
Day 16, 17 or 21	266	204	200*	167	[15]	[16**]	[21]	[14]
Day 23 or 24	266	224	189*	164**	[18]	[24**]	NA	NA
Platelet Counts (10^3 cells/µL) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	[26]	[14]
Day 23 or 24	NA	NA	NA	NA	NA	NA	[30]	[14]
Day 28	NA	NA	NA	NA	[66]	112	NA	NA
Day 34 or 35	270	280	268	206	322	309	NA	NA
Day 41 or 42	264	250	288	258	292	268	NA	NA
Day 48 or 49	274	239	312	269	314	273	NA	NA
Day 55 or 56	261	246	284	240	323	290	NA	NA
Day 57	272	260	278	224	327	296	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Reticulocytes (10^9 cells/L) - Main								
Pretest (Day -22)	58.0	36.7	52.4	50.9	52.2	51.1	67.5	58.0
Day 7	60.8	74.9	38.5	58.8	[19.4]	35.1	[17.3]	ND
Day 14	61.9	67.1	47.2	69.5	[16.5]	[14.8*]	[24.8]	ND
Day **16**, **17** or 21	51.2	65.4	44.8	57.5	[17.1]	[13.9**]	ND (Day 16)	ND (Day 17)
Day 23 or 24	56.4	59.1	40.4*	37.8	33.4	[26.2*]	NA	NA
Reticulocytes (10^9 cells/L) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	[13.6]	[13.4]
Day 23 or 24	NA	NA	NA	NA	NA	NA	[13.2]	[11.1]
Day 28	NA	NA	NA	NA	82.4	142.0	NA	NA
Day 34 or 35	51.6	82.8	80.9	122.9	240.1	143.6	NA	NA
Day 41 or 42	70.3	95.2	90.6	144.0	201.5	130.4	NA	NA
Day 48 or 49	76.8	83.2	90.1	113.0	152.3	88.6	NA	NA
Day 55 or 56	42.1	87.9	63.7	117.4	114.4	95.4	NA	NA
Day 57	28.8	52.0	35.3	55.1	54.1	50.7	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
Red Blood Cells (10^6 cells/µL) - Main								
Pretest (Day -22)	6.35	6.13	6.74	6.04	6.25	6.55	6.43	6.21
Day 7	6.74	6.87	6.90	6.73	6.46	6.46	6.45	6.26
Day 14	6.82	6.88	7.03	6.78	6.02	6.18	6.61	6.25
Day 16, 17 or 21	6.52	6.62	6.91	6.33	[5.38]	[5.42*]	6.61	6.42
Day 23 or 24	6.58	6.54	6.45	6.16	[5.19]	5.87	NA	NA
Red Blood Cells (10^6 cells/µL) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	[5.85	5.45]
Day 23 or 24	NA	NA	NA	NA	NA	NA	[5.18]	[5.15]
Day 28	NA	NA	NA	NA	[5.16]	6.06	NA	NA
Day 34 or 35	6.07	6.84	6.98	6.85	[5.40]	5.76	NA	NA
Day 41 or 42	6.50	7.31	7.59	7.45	6.16	6.46	NA	NA
Day 48 or 49	6.98	7.28	7.26	7.70	6.62	6.48	NA	NA
Day 55 or 56	6.55	7.17	7.34	7.64	6.46	6.63	NA	NA
Day 57	6.26	6.96	6.80	7.04	6.26	5.98	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Hematology (continued)								
White Blood Cells (10^3 cells/µL) - Main								
Pretest (Day -22)	10.28	10.56	9.78	9.67	8.84	11.34	7.29	12.36
Day 7	11.80	8.89	9.68*	7.95	10.47	[6.86*]	9.86	9.67
Day 14	10.02	9.13	8.48*	8.29	7.56	[6.63*]	8.54	7.38
Day 16, 17 or 21	10.26	10.10	7.85*	8.12*	[3.26]	[2.96**]	[6.47]	[5.37]
Day 23 or 24	9.63	9.84	7.75**	[6.86**]	[3.48]	[4.07**]	NA	NA
White Blood Cells (10^3 cells/µL) - Recovery								
Day 21	NA	NA	NA	NA	NA	NA	7.36	[5.94]
Day 23 or 24	NA	NA	NA	NA	NA	NA	6.72	[6.08]
Day 28	NA	NA	NA	NA	6.07	9.40	NA	NA
Day 34 or 35	11.30	11.48	9.97	9.45	9.66	9.66	NA	NA
Day 41 or 42	10.86	11.15	10.48	9.91	9.85	9.86	NA	NA
Day 48 or 49	10.62	9.84	8.84	9.21	10.88	8.02	NA	NA
Day 55 or 56	11.06	10.98	10.44	9.46	12.81	7.98	NA	NA
Day 57	9.01	8.58	8.92	7.43	8.68	6.78	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Coagulation								
Fibrinogen (mg/dL) - Main								
Pretest	249	248	225	315	212	245	181	286
Day 16 or 17	NA	NA	NA	NA	NA	NA	[335]	[436]
Day 23 or 24	174	188	181	216	[369]	[347**]	NA	NA
Fibrinogen (mg/dL) - Recovery								
Day 23 or 24	NA	NA	NA	NA	NA	NA	242	346
Day 57	158	188	155	197	162	200	NA	NA

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Bone Marrow Evaluation (Smears)								
M:E ratio - Main								
Day 16 or 17	NA	NA	NA	NA	NA	NA	[252] †	[10.73] †
Day 23 or 24	NA	NA	NA	NA	[0.94] §	[0.61] §	NA	NA
Day 29	1.13	1.34	1.28	1.08	NA	NA	NA	NA
M:E ratio - Recovery								
Day 23 or 24	NA	NA	NA	NA	NA	NA	1.08‡	0.87‡
Day 57	1.20	1.30	1.10	1.33	1.04#	1.13#	NA	NA

† 50 mg/kg/day: All 3 females evaluated on Day 16 had low cellularity, erythroid hypocellularity, myeloid shift to maturity. Only 1 male was evaluated (Day 17) in this group. This male had low cellularity, erythroid hypocellularity, myeloid shift to maturity, blood contamination. Unable to evaluate other 2 males at 50 mg/kg/day; blood, rare marrow precursor cells noted in both.

§ 17 mg/kg/day: Myeloid shift to immaturity was noted for 1 female and myeloid hypocellularity noted in 2 females. Only 1 male was evaluated (Day 24) in this group. This male had myeloid shift to immaturity, myeloid hypocellularity, blood contamination. Unable to evaluate other 2 males at 17 mg/kg/day due to excess blood contamination in both and high fat content in 1 male.

‡ 50 mg/kg/day: By recovery Day 23/24, bone marrow slides were of good quality and cellularity, with M:E ratios minimally lower than control in both sexes, likely due to the robust early regeneration of both erythroid and myeloid series cells with a more pronounced increase in the erythroid series. Male lymphocyte percentage was mildly lower than control, likely a result of robust regeneration of the erythroid and myeloid series precursor cells while female percentages were similar to control. Megakaryocytes were frequently present with expected maturation stages noted at low power with morphology appearing normal. These finding were suggestive of a complete bone morrow recovery without a peripheral erythrocyte, leukocyte, or platelet count recovery by this timepoint.

17 mg/kg/day: By recovery Day 57, bone marrow smears were of good quality and cellularity, M:E ratios, lymphocyte percentages, and megakaryocytes numbers and morphology similar to control, indicating complete recovery.

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Bone Marrow Evaluation (Smears) (continued)								
% Lymphocytes - Main								
Day 16 or 17	NA	NA	NA	NA	NA	NA	[26.5]	[16.5]
Day 23 or 24	NA	NA	NA	NA	[24.1]	5.0	NA	NA
Day 29	10.6	7.3	9.9	8.8	NA	NA	NA	NA
% Lymphocytes - Recovery								
Day 23 or 24	NA	NA	NA	NA	NA	NA	10.2	2.5‡
Day 57	9.6	11.7	9.5	9.0	5.7	6.7	NA	NA
Serum Biochemistry – Main & Recovery	-	-	-	-	-	-	-	-
Urinalysis – Main & Recovery	-	-	-	-	-	-	-	-
Organ Weights – Main & Recovery	-	-	-	-	-	-	-	-

‡ Male lymphocyte percentage was mildly lower, likely a result of robust regeneration of the erythroid and myeloid series precursor cells. Both males at 50 mg/kg/day (Day 24) also had decreased lymphocytes. Collectively, finding were suggestive of a complete bone morrow recovery without a peripheral erythrocyte, leukocyte, or platelet count recovery by this timepoint.

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Gross Pathology (Incidence) - Main								
Cecum (No. Examined)	3		3		3		3	
Focus	0		0		[2]		[1]	
Colon	3	3	3	3	3	3	3	3
Focus	0	0	0	0	[3]	[3]	[1]	[1]
Oral Mucosa, Buccal (No. Examined)		0		0		0		1
Discolored								[1]
Esophagus (No. Examined)		3		3		3		3
Focus		0		0		0		[1]
Gallbladder (No. Examined)		3		3		3		3
Focus		0		0		0		[1]
Mediastinal tissue		0		0		0		1
Discolored								[1]
Penis (No. Examined)		0		0		0		1
Focus								[1]

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Gross Pathology (Incidence) – Main, continued								
Rectum (No. Examined)	3	3	3	3	3	3	3	3
Focus	0	0	0	0	[1]	0	0	[1]
Stomach (No. Examined)	3		3		3		3	
Focus	0		0		0		[1]	
Thymus (No. Examined)		3		3		3		3
Discolored		0		0		0		[1]
Urinary Bladder		3		3		3		3
Discolored		0		0		0		[1]
Gross Pathology (Incidence) – Recovery								
Cecum (No. Examined)		2		2		2		2
Focus		0		0		0		[2]
Colon (No. Examined)		2		2		2		2
Focus		0		0		0		[2]
Duodenum (No. Examined)		2		2		2		2
Focus		0		0		0		[1]

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Gross Pathology (Incidence) – Recovery, (continued)								
Ileum (No. Examined)		2		2		2		2
Focus		0		0		0		[1]
Lymph Node, Mesenteric		2		2		2		2
Discolored		0		0		0		[1]
Size increased		0		0		0		[1]
Oral Mucosa, Buccal (No. Examined)		0		0		0		1
Discolored								[1]
Stomach (No. Examined)		2		2		2		2
Focus		1		0		0		[1]
Histopathology (Incidence): Bone Marrow - Main								
Femur (No. Examined)	3	3	3	3	3	3	3	3
Decreased Cellularity								
Mild						[1]		
Moderate					[2]		[1]	
Marked					[1]	[2]	[1]	[2]
Severe							[1]	[1]

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Histopathology (Incidence): Bone Marrow – Main (continued)								
Sternum (No. Examined)	3	3	3	3	3	3	3	3
Decreased Cellularity								
Mild						[1]		
Moderate					[2]		[1]	[1]
Marked					[1]	[2]	[1]	[1]
Severe							[1]	[1]
Histopathology (Incidence): Bone Marrow – Recovery								
Femur (No. Examined)	2	2	2	2	2	2	2	2
Decreased Cellularity								
Mild							[1]	
Moderate							[1]	[1]
Marked								[1]
Sternum (No. Examined)	2	2	2	2	2	2	2	2
Decreased Cellularity								
Moderate							[2]	[2]

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Histopathology (Incidence) – Main								
Brain – Hemorrhage, Cerebellum[e]								
Minimal						[1]		
Cecum – Hemorrhage								
Minimal					[2]			
Colon – Hemorrhage								
Minimal					[1]	[2]	[1]	
Mild								[1]
Esophagus								
Erosion, minimal								[1]
Hemorrhage, minimal								[1]
Gallbladder - Hemorrhage[e]								
Minimal								[1]
Heart - Hemorrhage[e]								
Mild								[1]

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Histopathology (Incidence) – Main (continued)								
Mediastinal Tissue - Hemorrhage[e]								
Marked								[1]
Oral Mucosa, buccal – Erosion/Ulcer								
Moderate								[1]
Penis - Hemorrhage[e]								
Minimal								[1]
Rectum – Hemorrhage								
Minimal				1		[1]	[1]	[1]
Mild					[1]	[1]		
Moderate								[1]
Spinal Cord, Thoracic – Hemorrhage[e]								
Minimal								[1]
Stomach, pylorus – Hemorrhage								
Minimal							[1]	

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Histopathology (Incidence) – Main (continued)								
Thymus, interstitium - Hemorrhage[e]								
Marked								[1]
Urinary Bladder - Hemorrhage[e]								
Moderate								[1]
Histopathology (Incidence) - Recovery								
Cecum - Hemorrhage								
Minimal			1					[1]
Mild								[1]
Colon - Hemorrhage								
Minimal								[1]
Mild								[1]
Duodenum - Hemorrhage								
Minimal		1						[1]
Ileum - Hemorrhage								
Minimal								[2]

Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.**: TT #[redacted]-7815 [Ref. 4.2.3.2: TT[redacted]7815FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		6		17		50	
Number of Animals – Main	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Number of Animals – Recovery	F:2	M:2	F:2	M:2	F:2	M:2	F:2	M:2
Noteworthy Findings (continued)								
Histopathology (Incidence) – Recovery (continued)								
Spinal Cord, Thoracic – Hemorrhage[e]								
Minimal								[1]
Stomach, pylorus – Hemorrhage								
Minimal								[1]

No noteworthy findings; [ ] Test article related change based on incidence and/or severity; D Decreased; Euth Euthanized (no data available);
MOV molnupiravir MK 4482 (EIDD 2801); NA Not applicable; ND Not Determined; NE Group not examined; NHC N hydroxycytidine (EIDD 1931).
*p<0.05 **p <0.01

a Plasma samples from control animals were collected at all timepoints, but only the 1 hr sample was analyzed. No data presented.
b See explanation of duration of dosing, treatment necropsy, recovery necropsy on first page of Sec. 2.6.7.7D
c Additional comparisons to control weights not presented due to differences in duration of dosing across groups.
d Control and treatment group values are mean absolute values or mean percents.
e The extra gastrointestinal sites involved single animals. All of the hemorrhage appeared as extravasation of erythrocytes without evidence of cellular infiltrates suggesting that they occurred just around euthanasia.

Sec. 2.6.7.8A Genotoxicity – In Vitro: Report Title: Bacterial Reverse Mutation Assay (TT #[redacted]-7851)

Test Article: NHC

Test for Induction of: Reverse mutation to wild type in bacteria cells **Strains:** *Salmonella typhimurium* (TA98, TA100, TA 1535, TA1537), *Escherichia coli* (WP2 *uvrA*) **Metabolizing System:** Aroclor induced rat liver S9, 50 µL/plate **Treatment:** Approximately 48 hours	**No. of Independent Assays:** 1 **No. of Replicate Cultures:** 2 per dose point **No. of Cells Analyzed/Culture:** Not applicable **Vehicle for Positive Controls:** Water (sodium azide) or DMSO (all others) **Vehicle for Test Article**: DMSO	**Study No**.: TT #[redacted] 7851 **Location in CTD:** [Ref. 4.2.3.3.1: TT[redacted]7851FIN] **GLP Compliance**: No **Date of Treatment:** [redacted]

Cytotoxic Effects: Without metabolic activation, toxicity was observed as inhibition of revertant growth in strains TA98, TA100, and TA1537 at concentrations ≥500 µg/plate, and in strain TA1535 at concentrations ≥1500 µg/plate. With metabolic activation, toxicity was observed as inhibition of revertant growth in strains TA98, TA100, TA1535, and TA1537 at concentrations ≥1500 µg/plate. (Cytotoxicity is defined as at least moderately reduced background lawn or 50% reduction in revertants compared to negative control.)
Genotoxic Effects†: Positive in *Escherichia coli* strain WP2 *uvrA* at concentrations ≥5 µg/plate with and without metabolic activation.

†Criteria for a positive result are (1) a 2 fold (TA98, TA100, WP2 *uvr*A) and 3 fold (TA1535 and TA1537) or greater increase in number of revertant colonies over control, and (2) above the corresponding acceptable vehicle control range.

Test Article	Dose (µg/plate)	Mutagenicity Assay Revertant Colony Counts (Mean of 2 Plates ± SD)				
		Salmonella typhimurium				*Escherichia coli*
		TA98	TA100	TA1535	TA1537	WP2 *uvrA*
Without Metabolic Activation						
Control (DMSO)	50 µL/plate	11±2	92±2	13±5	4±2	18±3
NHC	1.5	9±0	92±13	16±2	8±4	27±7
NHC	5.0	16±5	102±26	14±2	9±0	53±2*
NHC	15	13±3	78±8	12±1	8±3	90±30*
NHC	50	17±0	77±21	11±9	11±5	97±7*
NHC	150	17±6	65±14	17±4	14±4	131±47*
NHC	500	2±1	13±8	8±3	0±0	252±2*
NHC	1500	1±1	0±0	0±0	0±0	197±58*
NHC	5000	0±0	0±0	0±0	0±0	199±37*
2 Nitrofluorene	1.0	200±24	NA	NA	NA	NA
Sodium azide	1.0	NA	339±54	588±21	NA	NA
9 aminoacridine	75	NA	NA	NA	398±11	NA
Methylmethanesulfonate	1000	NA	NA	NA	NA	264±30

Sec. 2.6.7.8A Genotoxicity – In Vitro Study No.: TT #[redacted]-7851 [Ref. 4.2.3.3.1: TT[redacted]7851FIN] (Continued)

Test Article	Dose (µg/plate)	Mutagenicity Assay Revertant Colony Counts (Mean of 2 Plates ± SD)				
		Salmonella typhimurium				*Escherichia coli*
		TA98	TA100	TA1535	TA1537	WP2 *uvrA*
With Metabolic Activation						
Control (DMSO)	50 µLplate	19±4	185±20	15±6	6±1	41±6
NHC	1.5	19±2	178±2	10±4	5±0	64±19
NHC	5.0	24±4	173±14	12±1	5±4	141±15*
NHC	15	25±6	175±52	14±4	8±6	263±6*
NHC	50	23±5	173±1	17±1	9±4	312±30*
NHC	150	28±2	175±6	22±3	11±1	330±9*
NHC	500	10±0	173±16	16±1	6±1	258±94*
NHC	1500	0±0	0±0	3±3	1±1	204±37*
NHC	5000	0±0	0±0	0±0	0±0	247±81*
2 aminoanthracene	2.0	569±190	662±53	152±23	89±9	NA
2 aminoanthracene	15	NA	NA	NA	NA	317±11

NA Not Applicable; NHC N hydroxycytidine (EIDD 1931)

* Positive dose

Sec. 2.6.7.8B Genotoxicity – In Vitro: Report Title: Bacterial Reverse Mutation Assay (TT #[redacted]-7810)

Test Article: Molnupiravir

Test for Induction of: Reverse mutation to wild type in bacteria cells **Strains:** *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA102), *Escherichia coli* (WP2 *uvrA*) **Metabolizing System:** Aroclor induced rat liver S9 (1.4%) **Treatment:** Approximately 48 hours	**No. of Independent Assays:** 2 **No. of Replicate Cultures:** 3 per dose point **No. of Cells Analyzed/Culture:** Not applicable **Vehicle for Positive Controls:** DMSO **Vehicle for Test Article**: DMSO	**Study No**.: TT #[redacted] 7810 **Location in CTD:** [Ref. 4.2.3.3.1: TT[redacted]7810FIN] **GLP Compliance**: Yes [redacted]) **Date of Treatment:** [redacted] (range finding assay); [redacted] (mutagenicity assay); [redacted] (repeat mutagenicity assay in TA1535 +S9)
Dose Selection: The concentrations tested in the range finding assay were 1.0, 5.0, 10, 50, 100, 500, 1000, and 5000 µg/plate in strains TA100, TA102, and WP2 *uvrA*. Precipitates were not observed in any strain either with or without metabolic activation. Overgrown background lawns were observed at ≥ 100 µg/plate in TA102 with metabolic activation. Cytotoxicity was observed at ≥ 500 µg/plate in TA100 and at 5000 µg/plate in TA102 with metabolic activation.		
Additional Comments Regarding Test: For strain TA1535 with metabolic activation, cytotoxicity or precipitates were not observed in the mutagenicity assay; therefore, the strain was repeated up to 5000 µg/plate.		
Cytotoxic Effects: With metabolic activation, toxicity was observed at ≥ 500 µg/plate in TA1537 and TA100; at 1000 µg/plate in TA98; and at ≥1000 µg/plate in TA1535. (Cytotoxicity is defined as >50% reduction in mean number of revertant colonies compared to negative control or a significant reduction in the background lawn (> 50% clearing)).		
Genotoxic Effects†: Positive at ≥ 25.0 µg/plate in strains TA102 and WP2 *uvrA* with metabolic activation; ≥ 500 µg/plate in strain WP2 *uvrA* without metabolic activation; and ≥1000 µg/plate in strain TA102 without metabolic activation. †Criteria for a positive result are 2 fold (TA100 and TA102) and 3 fold (TA98, TA1535, TA1537, and WP2 uvrA) or greater increase in number of revertant colonies over control in at least 2 or more successive concentrations or repeatable at a single concentration.		

Sec. 2.6.7.8B Genotoxicity – In Vitro

Study No.: TT #[redacted]-7810 [Ref. 4.2.3.3.1: TT[redacted]7810FIN] (Continued)

Test Article	Dose (µg/plate)	Mutagenicity Assay Revertant Colony Counts (Mean of 3 Plates ± SD)					
		Salmonella typhimurium					*Escherichia coli*
		TA98	TA100	TA1535	TA1537	TA102	WP2 *uvrA*
Without Metabolic Activation							
Control (DMSO)	0.1 mL/plate	9±4	57±12	6±1	4±3	312±12	27±14
MOV	25.0	NT	NT	NT	NT	269±29	31±5
MOV	50.0	10±2	58±10	7±3	6±3	302±37	43±7
MOV	100	11±5	52±5	7±2	3±1	319±24	40±11
MOV	250	10±1	62±17	7±4	4±2	464±12	60±3
MOV	500	12±6	52±6	9±3	4±1	507±43	89±8*
MOV	1000	18±2	58±4	6±2	6±3	703±13*	148±19*
MOV	2500	12±5	50±6	6±2	6±3	956±14*	264±32*
MOV	5000	22±2	55±16	7±2	5±4	1270±55*	491±85*
2 Nitrofluorene	2.5	541±106	NT	NT	NT	NT	NT
Sodium azide	1.0	NT	201±22	378±11	NT	NT	NT
ICR 191 acridine	0.5	NT	NT	NT	171±13	NT	NT
4 Nitroquinoline N oxide	2.0	NT	NT	NT	NT	1211±55	836±41

Sec. 2.6.7.8B Genotoxicity – In Vitro

Study No.: TT #[redacted]-7810 [Ref. 4.2.3.3.1: TT[redacted]7810FIN] (Continued)

Test Article	Dose (µg/plate)	Mutagenicity Assay Revertant Colony Counts (Mean of 3 Plates ± SD)					
		Salmonella typhimurium					*Escherichia coli*
		TA98	TA100	TA1535	TA1537	TA102	WP2 uvrA
With Metabolic Activation							
Control (DMSO)	0.1 mL/plate	11±5	54±5	8±2	5±2	308±7	34±10
MOV	1.0	15±2	50±10	7±4	5±2	NT	NT
MOV	2.5	17±2	47±11	6±2	3±3	NT	NT
MOV	5.0	16±3	57±10	9±1	5±3	NT	NT
MOV	10.0	15±2	56±9	8±2	4±2	NT	NT
MOV	25.0	30±3	52±6	8±3	4±1	949±168*	254±28*
MOV	50.0	25±11	47±2	8±1	5±3	977±299*	477±23*
MOV	100	22±21	45±2	9±2	2±1	1534±90*	590±147*
MOV	250	25±10	36±6	10±1	3±3	1768±300[c]*	1054±126*
MOV	500	15±10	24±16	16±2	1±1[a]	1433±216[b]*	1499±249*
MOV	1000	5±6	7±8	12±2	1±1[a]	1117±224[b]*	1853±162*
MOV	2500	NT	NT	NT	NT	578±307[b]*	1850±172*
MOV	5000	NT	NT	NT	NT	749±289[b]*	1995±726*
2 Aminoanthracene	2.5	862±146	501±152	129±20	39±6	NT	NT
2 Aminoanthracene	10.0	NT	NT	NT	NT	1495±460	224±14

Sec. 2.6.7.8B Genotoxicity – In Vitro

Study No.: TT #[redacted]-7810 [Ref. 4.2.3.3.1: TT[redacted]7810FIN] (Continued)

Test Article	Dose (µg/plate)	Mutagenicity Assay Revertant Colony Counts (Mean of 3 Plates ± SD)
		Salmonella typhimurium
		TA1535
With Metabolic Activation		
Control (DMSO)	0.1 mL/plate	8±3
MOV	50.0	14±2
MOV	100	13±6
MOV	250	14±3
MOV	500	13±3
MOV	1000	2±2
MOV	2500	0±0
MOV	5000	0±0
2 Aminoanthracene	2.5	223±20

DMSO Dimethyl sulfoxide; NT Not tested; MOV Molnupiravir MK 4482 (EIDD 2801)

a Slightly reduced background lawn
b Overgrown background lawn
c Slightly overgrown background lawn
* Positive dose

Sec. 2.6.7.8C Genotoxicity – In Vitro: Report Title: In Vitro Micronucleus Assy in TK6 Cells (TT #[redacted]-7806)

Test Article: Molnupiravir

Test for Induction of: Micronuclei in TK6 cells **Strains:** TK6 human lymphoblastoid cells **Metabolizing System:** Aroclor-induced rat liver S9 **Treatment:** 4 hr (±S9) with 40 hour recovery (harvested at 44 hours after beginning of treatment); 27 hr (-S9) with no recovery (harvested at 27 hours after beginning of treatment)	**No. of Cells Analyzed/Culture:** 2000 cells per concentration **Vehicle for Positive Controls:** DMSO **Vehicle for Test Article**: DMSO	**Study No**.: TT #[redacted]-7806 **Location in CTD:** Section [Ref. 4.2.3.3.1: TT[redacted]7806FIN] **GLP Compliance**: Yes ([redacted]) **Date of Treatment:** [redacted] (range-finding assay); [redacted] (micronucleus assay); [redacted] (repeat micronucleus assay)
Dose Selection: Based on the results of the range-finding assay, target concentrations selected for the micronucleus assay ranged from 20.6 to 330 µg/mL for the 4-hour treatment without metabolic activation and from 2.58 to 330 µg/mL for the 4-hour treatment with metabolic activation and the 27-hour treatment without metabolic activation; 330 µg/mL equals ~1 mM, the regulatory maximum dose.		
Additional Comments Regarding Test: Due to a dosing error, the initial micronucleus assay was dosed 10X lower than targeted; actual concentrations ranged from 2.06 to 33.0 µg/mL for the 4-hour treatment (-S9) and from 0.258 to 33.0 µg/mL for the 4-hour (+S9) and 27-hour treatment (-S9). The assay was repeated at the originally intended concentrations.		
Cytotoxic Effects: See tables below.		
Genotoxic Effects†: None. No statistically significant test article-related increase in micronucleated cells was noted. The percent of micronucleated cells in vehicle and positive control cultures were comparable to the historical control data. †The test article would be considered positive for inducing micronuclei if a statistically significant increase ($p \leq 0.05$) in the mean percentage of micronucleated cells was observed at 1 or more dose levels. If a significant increase was seen at 1 or more dose levels, a dose-response should be observed. A response would be considered statistically significant for dose-response trend in the Cochran-Armitage test if $p \leq 0.05$. At least 1 concentration should be increased outside the historical control range of the vehicle control.		

Sec. 2.6.7.8C Genotoxicity – In Vivo **Study No.:** TT #[redacted]-7806 [Ref. 4.2.3.3.1: TT[redacted]7806FIN] (Continued)

Without Metabolic Activation

Treatment µg/mL	Treatment Time (Hr)	%Cytotoxicity	Mean %MN	Mean Fold Increase	Trend[a]
DMSO (1%)	4	0	0.70	1.00	NA
Mitomycin C 0.125	4	23	3.70**	5.29	NA
MOV 8.25	4	2	0.70	1.00	-
MOV 16.5	4	2	0.65	0.93	0.9517
MOV 33.0	4	4	0.70	1.00	-
Without Metabolic Activation (Repeat Assay)					
DMSO (1%)	4	0	0.45	1.00	NA
Mitomycin C 0.125	4	24	3.10**	6.89	NA
MOV 82.5	4	12	0.60	1.33	-
MOV 165	4	18	0.45	1.00	0.8295
MOV 330	4	23	0.45	1.00	-

DMSO Dimethylsulfoxide; MN Micronucleated cells; MOV Molnupiravir MK 4482 (EIDD 2801)
*p≤0.05, **p≤0.01 using Fisher's Exact Test 1 Tailed Test
a Trend: A Cochran Armitage Test was performed on the number of cells with micronuclei. ≤0.05 significant.

Sec. 2.6.7.8C Genotoxicity – In Vivo

Study No.: TT #[redacted]-7806 [Ref. 4.2.3.3.1: TT[redacted]7806FIN] (Continued)

Without Metabolic Activation

Treatment µg/mL	Treatment Time (Hr)	%Cytotoxicity	Mean %MN	Mean Fold Increase	Trend[a]
DMSO (1%)	27	0	0.80	1.00	NA
Vinblastine Sulfate 0.003	27	49	9.15**	11.44	NA
MOV 24.8	27	10	0.75	0.94	-
MOV 28.9	27	11	0.60	0.75	0.7236
MOV 33.0	27	12	0.75	0.94	-
Without Metabolic Activation (Repeat Assay)					
DMSO (1%)	27	0	0.35	1.00	NA
Vinblastine Sulfate 0.003	27	44	7.70**	22.00	NA
MOV 2.58	27	0	0.45	1.29	-
MOV 61.9	27	26	0.40	1.14	0.2956
MOV 248	27	58	0.60	1.71	-

DMSO Dimethylsulfoxide; MN Micronucleated cells; MOV Molnupiravir MK 4482 (EIDD 2801)
*p≤0.05, **p≤0.01 using Fisher's Exact Test 1 Tailed Test
a Trend: A Cochran Armitage Test was performed on the number of cells with micronuclei. ≤0.05 significant.

Sec. 2.6.7.8C Genotoxicity – In Vivo

Study No.: TT #[redacted]-7806 [Ref. 4.2.3.3.1: TT[redacted]7806FIN] (Continued)

With Metabolic Activation

Treatment µg/mL	Treatment Time (Hr)	%Cytotoxicity	Mean %MN	Mean Fold Increase	Trend[a]
DMSO (1%)	4	0	0.70	1.00	NA
Cyclophosphamide 11.9	4	39	5.30**	7.57	NA
MOV 24.8	4	42	0.50	0.71	-
MOV 28.9	4	35	0.75	1.07	0.901
MOV 33.0	4	36	0.65	0.93	-
With Metabolic Activation (Repeat Assay)					
DMSO (1%)	4	0	0.35	1.00	NA
Cyclophosphamide 11.9	4	64	5.95**	17.00	NA
MOV 2.58	4	2	0.45	1.29	-
MOV 20.6	4	28	0.55	1.57	0.5501
MOV 124	4	56	0.45	1.29	-

DMSO Dimethylsulfoxide; MN Micronucleated cells; MOV Molnupiravir MK 4482 (EIDD 2801)
*p≤0.05, **p≤0.01 using Fisher's Exact Test 1 Tailed Test
a Trend: A Cochran Armitage Test was performed on the number of cells with micronuclei. ≤0.05 significant.

Sec. 2.6.7.9A Genotoxicity – In Vivo: Report Title: An In Vivo Micronucleus Induction Assay of MOV by Oral Gavage in Sprague Dawley Rats (TT #[redacted]-7816)

Test Article: Molnupiravir

Test for Induction of: Micronuclei in rat bone marrow polychromatic erythrocytes **Species/Strain:** Rat/Crl:CD(SD) **Age:** 7 weeks **Cells Evaluated:** Polychromatic erythrocytes (PCE) **No. of Cells Analyzed/Animal:** 4000 PCE	**Treatment Schedule:** Once daily for 2 consecutive days for vehicle and test article groups; once on Day 2 for positive control group. **Sampling Time:** 18-24 hrs after the last dose for treatment groups; 24 hours after single dose for positive control group. **Method of Administration:** Oral gavage **Vehicle/Formulation**: 1% methylcellulose (400 cps) in deionized water	**Study No.:** TT #[redacted]-7816 **Location in CTD:** Section [Ref. 4.2.3.3.2: TT[redacted]7816FIN] **GLP Compliance:** Yes [redacted]) **Date of First Dose:** [redacted]
Dose Selection: Dose levels were selected based on repeat-dose studies in Sprague Dawley rats in which a no-observed-adverse-effect level (NOAEL) of 500 mg/kg was reported (TT #[redacted]-7814). In a previous single-dose study, MOV was tolerated after a single oral dose at 2000 mg/kg (TT #[redacted]-7825). Therefore, in an attempt to dose up to the regulatory maximum dose level of 2000 mg/kg/day, dose levels of 0, 500, 1000 and 2000 mg/kg/day were selected for this study.		
Additional Comments Regarding Test: None		
Cytotoxic Effects: No bone marrow cytotoxicity (decreases in PCE:TE ratio) was noted in any male or female rats at any dose level.		
Genotoxic Effects†: None. MOV did not produce statistically significant or dose-dependent increases in the %MN-PCEs in male or female rats at any dose level compared to the vehicle controls. †The test article would be considered positive for induction of micronuclei if (1) at least one treatment group exhibited a statistically significant increase in % MN-PCEs as compared with the concurrent negative control ($p \leq 0.05$); and (2) the increase was dose-related ($p \leq 0.05$); and (3) any increase was outside the 95% control interval of the historical negative control data. There were statistically significant increases in micronucleated PCE in positive control animals treated with cyclophosphamide monohydrate demonstrating the acceptability of the assay.		
Evidence of Exposure: Test article-related lower body weight gains were noted in the 1000 and 2000 mg/kg/day group males, and in the 500 and 2000 mg/kg/day group females from Days 1–3, compared to the control group. Test article-related lower food consumption was noted in all test article-treated males from Days 1–3, and in the 1000 and 2000 mg/kg/day group females from Days 1–3, compared to the control group. These observations demonstrated relevant evidence of exposure to MOV.		

Sec. 2.6.7.9A Genotoxicity – In Vivo **Study No.:** TT #[redacted]-7816 [Ref. 4.2.3.3.2: TT[redacted]7816FIN] (Continued)

Treatment Dose	Harvest Time (Hr)	Females Mean±SD %MN-PCEs	Females Mean±SD PCE:TE Ratio	Males Mean±SD %MN-PCEs	Males Mean±SD PCE:TE Ratio
1% Methylcellulose in deionized water 10 mL/kg	18-24	0.06±0.02	0.43±0.09	0.07±0.02	0.35±0.04
MOV 500 mg/kg/day	18-24	0.07±0.02	0.40±0.06	0.09±0.03	0.38±0.06
MOV 1000 mg/kg/day	18-24	0.08±0.03	0.38±0.08	0.08±0.03	0.41±0.04
MOV 2000 mg/kg/day	18-24	0.09±0.03	0.39±0.10	0.09±0.03	0.40±0.10
Cyclophosphamide 60 mg/kg/day	24	1.35±0.39[b]	0.31±0.06[a]	1.76±0.56[b]	0.32±0.03

Hr Hour; MN Micronucleated; NCE Normochromatic Erythrocyte; PCE Polychromatic erythrocytes; TE Total erythrocytes (PCE +NCE); MOV Molnupiravir MK 4482 (EIDD 2801).

a Statistically different than vehicle control $p \leq 0.05$ via ANOVA

b Statistically different than vehicle control $p \leq 0.01$ via ANOVA

Sec. 2.6.7.9B Genotoxicity – In Vivo: Report Title: In Vivo Mammalian Peripheral Blood Erythrocyte Pig-a Mutation Assay in Rat (TT #[redacted]-7808)

Test Article: Molnupiravir

Test for Induction of: phosphatidyl inositolglycan class A gene (pig-a) mutation on circulating blood erythrocytes **Species/Strain:** Rat/Crl:CD(SD) (males only) **Age:** 55 days old **Cells Evaluated:** Reticulocytes, Red Blood Cells	**Treatment Schedule:** 28 days for vehicle and treatment groups; 3 days for positive control group **Sampling Time:** Day 29 **Method of Administration:** Oral gavage **Vehicle/Formulation**: 1% methylcellulose (400 cps) in deionized water	**Study No.:** TT #[redacted]-7808 **Location in CTD:** Section [Ref. 4.2.3.3.2: TT[redacted]7808FIN] **GLP Compliance:** Yes ([redacted] **First Date of Dosing**: [redacted]
Dose Selection: The dose levels were selected based on the results of a one-month toxicity study with a 14-day recovery period (TT #[redacted]-7814) where doses up to 500 mg/kg/day were tolerated. In the single dose MTD/7-day dose range finding study in rats, the 2000 mg/kg dose was not well tolerated (TT #[redacted]-7825), with decreased body weight gain, clinical signs of toxicity and notable hematological changes. Consequently, 500 mg/kg was considered to be the MTD, and therefore was used as the top dose to be tested in the current study.		
Additional Comments Regarding Test: None		
Cytotoxic Effects: None. No substantial reduction in the %RETs was observed for any of the MOV-treated groups compared to the concurrent negative control value. Therefore, MOV did not cause cytotoxicity following administration of doses up to 500 mg/kg/day for 28 days to male rats.		
Genotoxic Effects: Eqivocal. Following 28 consecutive days of daily oral administration of MOV, an outlier test and statistical analysis were performed. Male rats did show statistically significant increases ($p \leq 0.05$) in the incidence of mutant RBCs and RETs for Group 4, dosed at 500 mg/kg/day, when compared to the concurrent negative control. In addition, Groups 2 and 3 were also found to be statistically significantly higher for the mutant RBCs values compared to Group 1. However, all values were within the 95% upper limit of the historical control values database. Moreover, the increase was not dose-related when evaluated with an appropriate trend test. Of note, two animals excluded from study selection had mutant RBC/RET values higher than the values obtained in Group 4, providing some guidance on biological variation in control values in the groups utilized in this study. Since not all criteria for a negative or positive response to induce mutagenicity were fullfilled, the results of the assay are therefore concluded as equivocal. According to the study protocol, all 3 criteria for positive or negative must be met, otherwise the assay results are categorized as 'equivocal', aligned with recommendations by the International Workshop on Genotoxicity Testing (IWGT) Workgroup for the in vivo Pig-a assay.		
Evidence of Exposure: Evidence to support systemic exposure of the test article at the tested dose levels was demonstrated in a previous one-month toxicity study using Sprague Dawley rats in TT #[redacted]-7814.		

Sec. 2.6.7.9B Genotoxicity – In Vivo

Study No.: TT #[redacted]-7808 [Ref. 4.2.3.3.2: TT[redacted]7808FIN] (Continued)

Treatment Dose	PREDOSE Mean±SD (% Difference from Vehicle Control) N=6 unless otherwise indicated %RET	Mutant RBCs per 10^6 Total RBCs	Mutant RETs per 10^6 Total RETs
1% Methylcellulose in deionized water 10 mL/kg	13.95±1.97	1.75±0.51	3.95±2.00
MOV 50 mg/kg/day	15.28±1.26 (10%)	1.47±0.46 (16%)	3.85±1.84 (3%)
MOV 150 mg/kg/day	14.40±1.27 (3%) N 5	1.26±0.23 (28%); N 5	3.66±1.44 (7%) N 5
MOV 500 mg/kg/day	14.18±0.71 (2%)	1.32±0.31 (25%) N 5	3.50±0.73 (11%)
Ethyl nitrosourea Positive Control 20 mg/kg/day	14.38±1.66 (3%) N 4	1.25±0.33 (29%) N 4	3.48±0.46 (12%) N 4
Treatment Dose	**Day 29** **%RET**	**Mutant RBCs per 10^6 Total RBCs**	**Mutant RETs per 10^6 Total RETs**
1% Methylcellulose in deionized water 10 mL/kg	4.02±0.62	0.87±0.26	4.97±1.56
MOV 50 mg/kg/day	4.45±0.48 (11%)	1.57 ^{A}±0.53 (81%)	5.52±1.83 (11%)
MOV 150 mg/kg/day	4.24±0.62 (6%) N 5	1.92 ^{A}± 0.53 (122%) N 5	7.80±1.54 (57%) N 5
MOV 500 mg/kg/day	3.66±0.61(9%) N 5	2.63 ^{A}±0.41 (203%) N 4	10.98 ^{A}±3.54 (121%) N 5
Ethyl nitrosourea Positive Control 20 mg/kg/day	3.95±0.53 (2%) N 4	156.63 ^{d}±26.04 (17972%) N 4	259.05 ^{d}±56.41 (5116%) N 4

RET Reticulocytes; RBCs Red blood cells; MOV Molnupiravir MK 4482 (EIDD 2801)
Statistically different than vehicle control value: A p≤0.05 (Dunnett); D p≤0.05 (Dunn); G ≤0.05 (Cochran Armitage's); a p≤0.05 (t test); d p≤0.05 (Wilcoxon)
There was no statistically significant trend and all values were within the 95% upper limit of the historical control values (see next page).

Sec. 2.6.7.9B Genotoxicity – In Vivo

Study No.: TT #[redacted]-7808 [Ref. 4.2.3.3.2: TT[redacted]7808FIN] (Continued)

Pig-a Assay in Peripheral Blood of Male Rats
Group Results
([redacted]-[redacted])

Historical Negative Control Data

	Mutant RBCs per 10^6 Total RBCs	Mutant RETs per 10^6 Total RETs	% of RETs over total erythrocytes
Mean ± SD	2.28 ± 1.92	4.09 ± 4.05	6.04 ± 2.73
Range (min-max)	0.40 - 7.78	0.57 - 16.08	2.92 - 13.38
Number of experiments	26	26	26
Upper limit, 95%	6.04	12.04	

Historical Positive Control Data*

	Mutant RBCs per 10^6 Total RBCs	Mutant RETs per 10^6 Total RETs	% of RETs over total erythrocytes
	Collection on Day 15		
Mean ± SD	77.37 ± 10.14	294.45 ± 47.96	4.71 ± 1.14
Range (min-max)	62.27 - 87.43	210.93 - 347.80	3.70 - 6.50
Number of experiments	6	6	6
	Collection on Day 29		
Mean ± SD	189.17 ± 13.15	314.15 ± 29.90	3.85 ± 0.23
Range (min-max)	166.87 - 201.87	281.87 - 361.20	3.57 - 4.13
Number of experiments	5	5	5

Abbreviations	Description
RBC	Red Blood Cells
RET	Reticulocytes
SD	Standard Deviation
*	Rats were treated using ethylnitrosourea (ENU 20 mg/kg/day) for 3 days

Sec. 2.6.7.9C Genotoxicity – In Vivo: Report Title: In Vivo Mutation Assay at the cII Locus in Big Blue® Transgenic F344 Rats (TT #[redacted]-9025)

Test Article: Molnupiravir

Test for Induction of: Mutation at the *cII* locus **Species/Strain:** Rat/transgenic Fischer 344 Big Blue® (male) **Age:** 8 weeks **Tissues Evaluated:** Liver and Bone Marrow	**Treatment Schedule:** 28 days **Sampling:** Day 31 (28 days of dosing and 3 additional days for mutation expression) **Method of Administration:** Oral gavage **Vehicle/Formulation**: 1% methylcellulose (400 cps) in deionized water	**Study No.:** TT #[redacted]-9025 **Location in CTD:** Section [Ref. 4.2.3.3.2: TT[redacted]9025FIN] **GLP Compliance:** Yes **First Date of Dosing**: [redacted]
Dose Selection: Dose levels were selected based on a 7-day oral dose range finding study in male Fischer 344 rats (TT #[redacted]-9027), in which the high dose of 500 mg/kg/day produced hunched posture and ruffled fur as well as hematological changes.		
Additional Comments Regarding Test: Assessment of tolerability was based on mortality, clinical observations, body weights, and food consumption. Animals were sacrificed by CO_2 overdose on Day 31. At necropsy, the liver (right medial lobe) and bone marrow were collected, flash frozen in liquid nitrogen and stored in a freezer set to -80°C. These tissues from the first five surviving animals/group were processed for DNA isolation and analysis of cII mutants, along with the DNA from the packaging positive controls. DNA isolated from previous positive control animals (F344 transgenic male rats exposed to N ethyl-N-nitrosourea (ENU) by oral gavage, at 20 mg/kg/day on 6 non-consecutive days) was used as a packaging positive control. These animals were collectively designated in the post life data as Group 5. ENU is a potent direct acting mutagen, demonstrated to be mutagenic in the target tissues.		
Genotoxic Effects: Negative. Treatment with MOV did not cause a statistically elevated mutant frequency at the *cII* gene in the liver or bone marrow of Big Blue® rats. The mutant frequencies for each tissue were also within the 95% confidence limits of the laboratory historical control range for each tissue. The ENU treatment produced a statistically significant increase in mutant frequencies for both tissues tested, demonstrating the utility of the test system to detect and quantify induced mutants, following exposure to a known direct acting mutagen.		
Evidence of Exposure: Hunched posture was observed in two animals at 500 mg/kg/day. A decrease in mean body weight gain was noted at 500 mg/kg/day (4.22% compared to the vehicle control group).		

Sec. 2.6.7.9C Genotoxicity – In Vivo **Study No.:** TT #[redacted]-9025 [Ref. 4.2.3.3.2: TT[redacted]9025FIN] (Continued)

	Mutant Frequency ± Standard Deviation ($x 10^{-6}$)	
Treatment Dose [a]	**Liver**	**Bone Marrow**
Vehicle Control (1% Methylcellulose in deionized water) 10 mL/kg N 5	34.0±1.9	33.0±11.9
MOV 50 mg/kg/day N 5	40.8±18.3	38.8±16.3
MOV 150 mg/kg/day N 5	35.7±17.1	24.4±6.0
MOV 500 mg/kg/day N 5	34.1±9.3	39.1±12.3
Positive Control (N ethyl N nitrosourea) [b] 20 mg/kg/day N 5	221.7±45.5*	434.2±61.6*

MOV Molnupiravir MK 4482 (EIDD 2801)
a Animals in the vehicle control and MOV dose groups were dosed for 28 days and necropsied on Day 31.
b Animals in the positive control group were dosed on Days 1, 2, 3, 10, 17, and 24, and necropsied on Day 31 (not run concurrently).
*Statistically significant (1 Way Anova, $p<0.001$).

Sec. 2.6.7.10 Carcinogenicity

No carcinogenicity studies have been completed.

Sec. 2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies

No non-pivotal reproductive and developmental toxicity studies have been conducted to date. Results of the GLP-compliant preliminary and definitive embryo-fetal developmental toxicity studies are presented in [Sec. 2.6.7.13A] through [Sec. 2.6.7.13D], and the non-GLP toxicokinetic study in nonpregnant rabbits is presented in [Sec. 2.6.7.17C].

Sec. 2.6.7.12A Reproductive and Developmental Toxicity (Fertility and Early Embryonic Development to Implantation): Report Title: A Fertility Study by Oral Gavage Administration in the Female Rat (TT #[redacted]-9000)

Fertility and Early Embryonic Development to Implantation

Design Similar to ICH 4.1.1? Yes
Species/Strain: Rat/Crl:CD(SD)
Age at Study Start: ~11 weeks old on first day of predose estrous cyclicity and ~13 weeks old on first dose day
Study Start Date : [redacted] (predose estrous initiation); [redacted] (dosing initiation)

Day of Mating: GD 0
Day of Cesarean-Section: GD 13
Method of Administration: Oral (gavage)
Dosing Volume: 10 mL/kg
Vehicle/Formulation: 1% Methylcellulose (400 cps) in deionized water

Test Article: Molnupiravir
Study Number: TT #[redacted]-9000
Location in CTD:
[Ref. 4.2.3.5.1: TT[redacted]9000FIN]
GLP Compliance: Yes[a]

Special Features: None

Treatment Interval (Females for fertility assessment): 2 weeks prior to cohabitation, during cohabitation (up to 21 days), and continuing to GD 7

Treatment Interval (Females for TK sampling): Day 15 (8 females per group)

Treatment Interval (Males): None

No-Observed-Effect Level: ≥500 mg/kg/day (female fertility parameters; female general toxicity parameters)

No-Observed-Adverse-Effect Level: ≥500 mg/kg/day (female fertility parameters; female general toxicity parameters)

		NHC: Females		
Daily Dose (mg/kg)	0 (Control):	100	250	500
Toxicokinetics – SD 15[b]				
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	14.9	61.4	157
C_{max} (μM)	NA	7.41	31.5	71.4
T_{max} (hr)	NA	0.500	1.00	1.00

Sec. 2.6.7.12A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9000 [Ref. 4.2.3.5.1: TT[redacted]9000FIN]

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control):	100	250	500
Number of Animals (Total)[b]	30	30	30	30
Number of Animals – Fertility Assessments	22	22	22	22
Noteworthy Findings				
Mortality	1[c]	0	0	0
Clinical Signs	-	-	-	-
Body Weight Change	-	-	-	-
Food Consumption	-	-	-	-
Reproductive Parameters				
Noteworthy Findings				
Mean Number of Cycles (Day 13→0)	2.1	2.4	2.5	2.5
Mean of Cycle Length (Day 13→0)	4.27	4.30	4.02	4.07
No. Females Cohabited	22	22	22	22
No. Females Bred	22	22	22	22
No. Pregnant Females	22	21	21	22
Confirmed Mating (Days 1-7)	22	21	21	22
Confirmed Mating (Days 8-14)	0	1	0	0
Confirmed Mating (Days 15-21)	0	0	1	0
Female Mating Index (%)	100.0	100.0	100.0	100.0

Sec. 2.6.7.12A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9000 [Ref. 4.2.3.5.1: TT[redacted]9000FIN]

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control):	100	250	500
Number of Animals – Fertility Assessments	22	22	22	22
Reproductive Parameters				
Fecundity Index (%)	100.0	95.5	95.5	100.0
Fertility Index (%)	100.0	95.5	95.5	100.0
Mean No. Corpora lutea/pregnant female	16.4	15.9	15.9	15.5
Mean No. Implantations/pregnant female	15.8	14.9	14.9	14.9
Mean No. of Dead embryos/pregnant female (L.M.)	1.1	0.9	0.5	0.8
Mean No. Live embryo/pregnant female	14.6	14.0	14.4	14.0
% Peri-implantation loss (L.M.)	3.73	5.67	7.59	4.48
% Postimplantation loss (L.M.)	6.98	6.51	7.40	5.29
Gross Examination[c,d]	-	-	-	-

– No noteworthy findings. GD Gestation Day; L.M. Litter Mean; MOV molnupiravir MK 4482 (EIDD 2801); NA Not applicable; NHC N hydroxycytidine (EIDD 1931)

Mating Index Mated females/females cohabited.
Fecundity Index Pregnant females/mated females.
Fertility Index Pregnant females/females cohabited.
% Peri implantation loss [(No. of corpora lutea no. of implantations)/(no. of corpora lutea)] × 100.
% Postimplantation loss [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100.

a GLP, [redacted].
b NHC concentrations in plasma from all control group animals were below the lower limit of quantitation.
c One control animal (N0. 7805) was euthanized on GD 6 due to opening or rupture of a mass on the right side of the neck. At necropsy, the mass appeared infected and the spleen enlarged.
d Limited to examination of the thoracic, abdominal and pelvic viscera.

Sec. 2.6.7.12B Reproductive and Developmental Toxicity (Fertility and Early Embryonic Development to Implantation): Report Title: A Fertility Study by Oral Gavage Administration in Male Rats (TT #[redacted]-9012)

Fertility and Early Embryonic Development to Implantation

Design Similar to ICH 4.1.1? Yes
Species/Strain: Rat/Crl:CD(SD)
Age at Study Start: Males: ~11 weeks
Study Start Date: [redacted]

Day of Mating: GD 0
Day of Cesarean-Section: GD 13
Method of Administration: Oral (gavage)
Dosing Volume: 10 mL/kg
Vehicle/Formulation: 1% Methylcellulose (400 cps) in deionized water

Test Article: Molnupiravir

Study Number: TT #[redacted]-9012
Location in CTD:
[Ref. 4.2.3.5.1: TT[redacted]9012FIN]
GLP Compliance: Yes[a]

Special Features: None

Treatment Interval (Females): None (22 untreated females/group)

Treatment Interval (Males): 14 days prior to cohabitation, during cohabitation, until the day prior to sacrifice (study day 46), (~6 weeks total).

No-Observed-Effect Level: ≥500 mg/kg/day for male fertility parameters and 250 mg/kg/day for general toxicity based on nonadverse decreases in mean body weights, body weight gains, and food consumption at 500 mg/kg/day, relative to controls.

No-Observed-Adverse-Effect Level: ≥500 mg/kg/day for both general toxicity and male fertility parameters

		NHC: Males		
Daily Dose (mg/kg)	0 (Control)	100	250	500
Toxicokinetics – SD 15[b,c]				
$AUC_{0\text{-}24\ hr}$ (μM•hr)	NA	45.6	179	463
C_{max} (μM)	NA	23.2	64.6	129
T_{max} (hr)	NA	1.00	1.00	1.00

Sec. 2.6.7.12B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-9012
[Ref. 4.2.3.5.1: TT[redacted]9012FIN] (continued)

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control)	100	250	500
Number of Males (Total)[c]	30	30	30	30
Number of Rats – Fertility Assessments	22	22	22	22
Noteworthy Findings				
Mortality	0	1[d]	0	0
Clinical Observations	-	-	-	-
Body Weight (g) – Day 47 (%)[e]	566.7	+0.2	-3.1	[-7.3]**
Body Weight Gain (g)[f]				
Day 1-47 (%)	199.5	-1.6	-10.6	[-21.3]**
Food Consumption[g]				
Day 4-8 (%)	30.4 g/day	0	-5.6	[-11.5]**
Day 1-14 (%)	30.2 g/day	+1.3	-2.7	[-8.6]*

Sec. 2.6.7.12B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-9012
[Ref. 4.2.3.5.1: TT[redacted]9012FIN] (continued)

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control)	100	250	500
Number of Males (Total)[b]	30	30	30	30
Number of Males – Fertility Assessments	22	22	22	22
Reproductive Parameters				
Noteworthy Findings				
No. Mated Males	22	22	22	22
No. Males Impregnated a Female	20	20	20	22
Male Mating Index (%)	100.0	100.0	100.0	100.0
Male Fertility Index (%)	90.9	90.9	90.9	100.0

Sec. 2.6.7.12B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-9012
[Ref. 4.2.3.5.1: TT[redacted]9012FIN] (continued)

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control)	100	250	500
Number of Males (Total)	30	30	30	30
Number of Rats – Fertility Assessments	22	22	22	22
Noteworthy Findings				
Maternal Performance				
No. Females Pregnant	20	20	20	22
No. Females with Live Embryos	20	20	20	22
No. Females with any Nonviable	6	7	8	10
No. Females with all Nonviable	0	0	0	0
Aborted	0	0	0	0
Maternal Reproductive Performance				
No. Females Cohabitated	22	22	22	22
No. Mated Females	22	21	22	22
Pre-coital Interval (Days) Mean	1.7	2.1	1.5	1.8
No. of Pregnant Females No Confirmed Mating	0	1	0	0
Confirmed Mating (Days 1-7)	22	21	22	22
Confirmed Mating (Days 8-14)	0	0	0	0
Female Mating Index (%)	100.0	100.0	100.0	100.0
Female Fecundity Index (%)	90.9	90.9	90.9	100.0
Female Fertility Index (%)	90.9	90.9	90.9	100.0

Sec. 2.6.7.12B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-9012
[Ref. 4.2.3.5.1: TT[redacted]9012FIN] (continued)

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control)	100	250	500
Number of Males (Total)	30	30	30	30
Number of Rats – Fertility Assessments	22	22	22	22
Noteworthy Findings				
Reproductive Parameters				
Females with Live Embryos	20	19	20	22
No. Corpora lutea/pregnant female	15.2	15.2	14.3	15.2
No. Implantations/pregnant female	14.6	14.4	13.9	14.1
Total No. of Embryos	14.6	14.4	13.9	14.1
No. of Live Embryos	14.3	14.0	13.0	13.5
No. of Dead Embryos	0.4	0.4	0.9	0.5
Postimplantation Loss	2.33	2.94	6.24	4.11
Gross Examination[h]	-	-	-	-

Sec. 2.6.7.12B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-9012
[Ref. 4.2.3.5.1: TT[redacted]9012FIN] (continued)

Fertility and Early Embryonic Development to Implantation

– No noteworthy findings; [ ] Test article related change; GD Gestation Day; MOV molnupiravir MK 4482 (EIDD 2801); NA Not applicable; NHC N hydroxycytidine (EIDD 1931)

Mating Index Mated rats/cohabited rats.
Fecundity Index Pregnant females/mated females.
Fertility Index Pregnant females/females cohabited.
% Peri implantation loss [(No. of corpora lutea no. of implantations)/(no. of corpora lutea)] × 100.
% Postimplantation loss [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100.
*p≤0.01 (Anova & Dunnett); **p≤0.01 (Anova & Dunnett)

a GLP, [redacted].

b NHC concentrations in plasma from all control group animals were below the lower limit of quantitation.

c Twenty two males/group were designated for fertility assessment; 8 males in the control group test article treated group were designated for TK analysis. Twenty two untreated females/group were assigned to main study.

d One male (No. 2533) from the main study was found dead prior to dosing on Study Day 44. This death was not considered test article related because of the single occurrence and lack of dose dependency. No remarkable clinical signs or changes in body weight were noted. All tissues appeared normal at necropsy, and presented with a moderate degree of autolysis.

e Body weights on Study Day 47. For control males, group mean is shown. For dose groups, percent differences from controls are shown.

f Day 1 47 body weight change: for control males, group mean is shown. For dose groups, percent differences from controls are shown

g Food consumption: for dose groups, percent differences from controls are shown.

h Gross examinations were limited to examination of the thoracic, abdominal, and pelvic viscera

Sec. 2.6.7.13A Reproductive and Developmental Toxicity (Effects on Embryo-Fetal Development): Report Title: Preliminary Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rats (TT #[redacted]-7054)

Design Similar to ICH 4.1.3? Yes
Species/Strain: Rat/Crl:CD(SD)
Age on GD 0: ~10 weeks
Study Start Date: [redacted]
Special Features: TK - GD 15 (8 females/dose group)

Day of Mating: GD 0
Day of Cesarean-Section: GD 21
Method of Administration: Oral (gavage)
Dosing Volume: 10 mL/kg
Vehicle/Formulation: Suspension in 1.0 % (w/v) methylcellulose in deionized water

Test Article: Molnupiravir
Study Number: TT #[redacted]-7054
Location in CTD: [Ref. 4.2.3.5.2: TT[redacted]7054FIN]
GLP: Yes[a]

Treatment Interval: GD 6 through 17 (females that survived until scheduled cesarean-section), GD 6 through 15 (females that survived until scheduled for TK blood collection)

No-Observed-Effect Level: Not Applicable

No-Observed-Adverse-Effect Level: Not Applicable

Daily Dose (mg/kg/day)	0 (Control)	100	200	500	1000
Maternal Toxicokinetics (GD 15) [b]			**MOV**		
$AUC_{0\text{-}24hr}$ (µM•hr)	NA	0.165	0.272	1.31	2.94
C_{max} (µM)	NA	0.116	0.215	0.614	0.827
T_{max} (hr)	NA	0.500	0.500	0.500	1.00
Maternal Toxicokinetics (GD 15) [b]			**NHC**		
$AUC_{0\text{-}24hr}$ (µM•hr)	NA	22.5	45.7	217	570
C_{max} (µM)	NA	12.1	26.0	103	207
T_{max} (hr)	NA	0.500	0.500	1.00	1.00

Sec. 2.6.7.13A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7054 [Ref. 4.2.3.5.2: TT[redacted]7054FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	200	500	1000
Number of Animals					
Total No. of Females[c]	16	16	16	16	16
No. Females Scheduled for Cesarean-Section	8	8	8	8	8
Noteworthy Findings					
Mortality (No. of Females)	0	0	0	0	2[d]
Physical Examinations	-	-	-	-	-
Body Weight Change (g) - Mean					
GD 6 to 10	23.4	24.8	21.3	22.4	[4.4]
GD 10 to 18	68.7	62.2	67.9	67.3	70.1
GD 6 to 18	92.1	87.0	89.2	89.9	81.2
GD 18 to 21	43.9	44.5	54.7	49.2	56.0
GD 6 to 21	136.0	131.4	143.9	139.0	137.2
GD 6 to Adj 21 (adjusted for gravid uterine weight)	54.5	48.8	53.4	51.9	54.9
Food Consumption (g/day) – Mean					
GD 8	20.9	21.5	21.3	19.5	[15.7]
GD 14	24.6	24.8	24.0	24.0	23.9
GD 20	26.1	26.6	27.7	27.4	29.9
Gross Examination[e]	-	-	-	-	-

Sec. 2.6.7.13A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7054 [Ref. 4.2.3.5.2: TT[redacted]7054FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	200	500	1000
Number of Animals					
Total No. of Females[c]	16	16	16	16	16
No. Females Scheduled for Cesarean-Section	8	8	8	8	8
No. Pregnant Females	8	8	8	7	8
No. Nonpregnant Females	0	0	0	1	0
Noteworthy Findings (continued)					
Reproductive Parameters (mean values)					
No. Examined Live Litters	8	8	8	7	6
No. Corpora lutea/pregnant female	11.6	11.6	14.0	12.7	13.4
No. Implantations/pregnant female	10.6	10.9	12.3	12.1	13.1
% Resorptions/implantations (L.M.)	6.3	6.3	3.8	4.7	[22.0]
% Dead fetuses/implantations (L.M.)	0.0	0.0	0.0	0.0	0.0
No. Live fetuses/pregnant female	9.9	10.3	11.8	11.6	10.7
% Peri-implantation loss (L.M.)	8.6	6.8	11.5	4.4	1.5
% Postimplantation loss (L.M.)	6.3	6.3	3.8	4.7	[22.0]
Fetal sex ratios (L.M.)	0.50	0.52	0.50	0.50	0.49
Live Fetal Weights (g)					
Females	5.82	5.80	5.57	[5.43]	[4.45]
Males	6.21	5.96	5.82	[5.54]	[4.57]

Sec. 2.6.7.13A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7054 [Ref. 4.2.3.5.2: TT[redacted]7054FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	200	500	1000
Noteworthy Findings (continued)					
Placental Morphology					
No. abnormal placentas/total examined [e]	0/79	0/82	0/94	0/81	0/75
Fetal Examinations					
External Examinations					
Live Fetuses/Litters Examined:	79/8	82/8	94/8	81/7	75/6
Absent eye bulge (M) (%L.M.)	0	0	0	0	[1 (1.7)]
Small eye bulge (M) (%L.M.)	0	0	0	0	[2 (2.6)]
Visceral Examinations					
Live Fetuses/Litters Examined:	79/8	82/8	94/8	81/7	75/6
Absent kidney (M) (%L.M.)	0	0	0	0	[2 (2.9)]
Coronal Examinations					
Live Fetuses/Litters Examined:	39/8	39/8	44/8	39/7	39/6
Absent eye (M) (%L.M.)	0	0	0	0	[2 (4.9)]
Small eye (M) (%L.M.)	0	0	0	0	[2 (4.9)]

Sec. 2.6.7.13A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7054 [Ref. 4.2.3.5.2: TT[redacted]7054FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	200	500	1000
Skeletal Examinations					
Live Fetuses/Litters Examined	79/8	82/8	94/8	81/7	75/6
Rib malformation (M)	0	0	1 (0.96)	0	[13 (19)]
Thoracic vertebrae malformation (M)	0	0	0	0	[1 (1.7)]
Lumbar vertebrae malformation (M)	0	0	0	0	[2 (2.9)]
Skull malformation (small eye socket) (M)	0	0	0	0	[1 (4.2)]
Cervical ribs (V)	2 (2.4)	0	5 (4.8)	5 (6.3)	[17 (23)]
Trace supernumerary ribs (V)	2 (2.6)	12 (13)	7 (7.4)	11 (14)	[17 (23)]
Fetal Ossification					
No. of ossified sacrocaudal vertebrae	10.8	10.6	10.4	10.2	[9.2]
Incomplete ossification					
Thoracic	1 (1.3)	0	0	1 (1.3)	[12 (15)]
Sternabra	1 (1.6)	2 (3.0)	0	0	[15 (21)]

– No noteworthy findings; [ ] Test article related change; #/# number affected/number examined.
Fetal sex ratio [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)]
% Peri implantation loss [(No. of corpora lutea no. of implantations)/(no. of corpora lutea)] × 100
% Postimplantation loss [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100
GD Gestation Day; L.M. Litter Mean; M Malformation; MOV molnupiravir MK 4482 (EIDD 2801); N/A Not applicable; NHC N hydroxycytidine (EIDD 1931); TK Toxicokinetics; V Variation
a GLP [redacted].
b Concentrations of MOV and NHC in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation.
c For each group, 8 females were designated for cesarean section and 8 females were designated for toxicokinetic blood collection.
d Two females in the 1000 mg/kg/day group were euthanized on GD 10 due to excessive toxicity [body weight loss of 25.6 g (11.7%) and 35.4 g (15.7%) between GD 6 and 10].
e Limited to examination of the thoracic and abdominal viscera.

Sec. 2.6.7.13B Reproductive and Developmental Toxicity (Effects on Embryo-Fetal Development): Report Title: Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rats (TT #[redacted]-7000)

Design Similar to ICH 4.1.3? Yes
Species/Strain: Rat/Crl:CD(SD)
Age on GD 0: ~10 weeks
Study Start Date: [redacted]
Special Features: TK - GD 15 (8 females/dose group)

Day of Mating: GD 0
Day of Cesarean-Section: GD 21
Method of Administration: Oral (gavage)
Dosing Volume: 10 mL/kg
Vehicle/Formulation: Suspension in 1.0 % (w/v) methylcellulose in deionized water

Test Article: Molnupiravir
Study Number: TT #[redacted]-7000
Location in CTD: [Ref. 4.2.3.5.2: TT[redacted]7000FIN]
GLP: Yes[a]

Treatment Interval: GD 6 through 17 (females that survived until scheduled cesarean-section), GD 6 through 15 (females that survived until scheduled for TK blood collection)

No-Observed-Effect Level: 250 mg/kg/day (maternal and developmental toxicity)

No-Observed-Adverse-Effect Level: 250 mg/kg/day for maternal and developmental toxicity, based on decreased body weight gain and transiently decreased food consumption and reduced fetal growth at 500 mg/kg/day.

Daily Dose (mg/kg/day)	0 (Control)	100	250	500
Maternal Toxicokinetics (GD 15)[b]			**NHC**	
$AUC_{0\text{-}24hr}$ (µM•hr)	NA	18.4	58.3	NC [c]
C_{max} (µM)	NA	11.4	34.2	NC [c]
T_{max} (hr)	NA	1.00	1.00	NC [c]

Sec. 2.6.7.13B Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7000 [Ref. 4.2.3.5.2: TT[redacted]7000FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	250	500
Number of Animals				
Total No. of Females [d]	28	28	28	28
No. Females Scheduled for Cesarean-Section	20	20	20	20
Noteworthy Findings				
Mortality (No. of Females)	0	0	0	0
Physical Examinations	-	-	-	-
Body Weight Change (g) - Mean				
GD 6 to 8	12.2	11.7	10.3	[7.3]
GD 8 to 18	83.5	86.4	83.1	80.4
GD 6 to 18	95.6	98.1	93.4	[87.6]
GD 18 to 21	45.9	45.8	46.4	43.3
GD 6 to 21	141.5	143.9	139.8	130.9
GD 6 to Adj 21 (adjusted for gravid uterine weight)	53.6	54.9	48.5	50.4
Food Consumption (g/day) – Mean				
GD 8	21.8	21.2	21.0	[18.9]
GD 14	25.2	25.0	24.5	23.9
GD 20	26.1	26.4	26.1	25.3
Gross Examination [e]	-	-	-	-

Sec. 2.6.7.13B Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7000 [Ref. 4.2.3.5.2: TT[redacted]7000FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	250	500
Number of Animals				
Total No. of Females [b]	28	28	28	28
No. Females Scheduled for Cesarean-Section	20	20	20	20
No. Pregnant Females	20	20	20	19
No. Nonpregnant Females	0	0	0	1
Noteworthy Findings (continued)				
Reproductive Parameters (mean values)				
No. Examined Live Litters	20	20	19	19
Resorbed or dead litter	0	0	1	0
No. Corpora lutea/pregnant female	12.9	13.1	13.7	12.8
No. Implantations/pregnant female	11.6	11.8	11.9	12.1
% Resorptions/implantations (L.M.)	7.0	4.7	10.3	7.0
% Dead fetuses/implantations (L.M.)	1.1	0.0	0.0	0.0
No. Live fetuses/pregnant female	10.8	11.3	11.2	11.2
% Peri-implantation loss (L.M.)	8.4	9.1	4.2	5.2
% Postimplantation loss (L.M.)	8.1	4.7	10.3	7.0
Fetal sex ratios (L.M.)	0.51	0.41	0.56	0.49
Live Fetal Weights (g)				
Females	5.75	5.68	5.58	[5.11]
Males	6.16	5.94	5.86	[5.33]

Sec. 2.6.7.13B Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7000 [Ref. 4.2.3.5.2: TT[redacted]7000FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	100	250	500
Noteworthy Findings (continued)				
Placental Morphology				
No. abnormal placentas/total examined	0 (0)[f]/216 (2)[f]	0/226	0/224	0/213
Fetal Examinations				
External Examinations	-	-	-	-
Live Fetuses/Litters Examined:	216/20	226/20	224/19	213/19
Visceral Examinations	-	-	-	-
Live Fetuses/Litters Examined:	113/19	121/20	117/19	112/19
Coronal Examinations	-	-	-	-
Live Fetuses/Litters Examined:	103/20	105/20	107/19	101/19
Skeletal Examinations	-	-	-	-
Live Fetuses/Litters Examined	113/19	121/20	117/19	112/19
Fetal Ossification				
No. of ossified sacrocaudal vertebrae	10.9	10.6	10.5	[10.0]

Sec. 2.6.7.13B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7000 [Ref. 4.2.3.5.2: TT[redacted]7000FIN] (Continued)

Effects on Embryo-Fetal Development

– No noteworthy findings; [ ] Test article related change; #/# number affected/number examined.
Fetal sex ratio [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)]
% Peri implantation loss [(No. of corpora lutea no. of implantations)/(no. of corpora lutea)] × 100
% Postimplantation loss [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100
GD Gestation Day; L.M. Litter Mean; M Malformation; N/A Not applicable; NC Not calculated; NHC N hydroxycytidine (EIDD 1931); TK Toxicokinetics; V Variation

a GLP [redacted].
b Concentrations of NHC in plasma from all control group animals were below the lower limit of quantitation.
c Plasma samples from the 500 mg/kg/group were excluded from toxicokinetic analysis due to inaccurate plasma sample volume collection. Toxicokinetic parameters at the 500 mg/kg/day dose can be ascertained from the pEFD study (TT #[redacted] 7054).
d For each group, 20 females were designated for cesarean section and 8 females were designated for toxicokinetic blood collection.
e Limited to examination of the thoracic and abdominal viscera.
f Number in parentheses represents placentas from dead fetuses.

Sec. 2.6.7.13C Reproductive and Developmental Toxicity (Effects on Embryo-Fetal Development): Report Title: Preliminary Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rabbits (TT #[redacted]-7064)

Design Similar to ICH 4.1.3? Yes
Species/Strain: Rabbit, Dutch Belted
Age on GD 0: ~25 to 30 weeks
Study Start Date: [redacted]
Special Features: TK - GD 15 (4 females/dose group)

Day of Mating: GD 0
Day of Cesarean-Section: GD 28
Method of Administration: Dosing Volume: 5 mL/kg
Vehicle/Formulation: 1.0 % Methylcellulose in deionized water

Test Article: Molnupiravir
Study Number: TT #[redacted]-7064
Location in CTD: [Ref. 4.2.3.5.2: TT[redacted]7064FIN]
GLP Compliance: Yes[a]

Treatment Interval: GD 7 through 19 (females scheduled for cesarean-section), GD 7 through 15 (females scheduled for TK blood collection)

No-Observed-Effect Level: NA

No-Observed-Adverse-Effect Level: NA

Daily Dose (mg/kg/day)	0 (Control)[b]	60	200[c]	500	1000
Maternal Toxicokinetics (GD 15)[d, e]			**MOV**		
$AUC_{0\text{-}24hr}$ (µM•hr)	NA	0.276	NR	0.506	0.702
C_{max} (µM)	NA	0.0444	NR	0.139	0.205
T_{max} (hr)	NA	2.63	NR	0.625	0.667

Sec. 2.6.7.13C Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7064 [Ref. 4.2.3.5.2: TT[redacted]7064FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	60	200	500	1000
Number of Animals					
Total No. of Females[d]	12	12	12	12	12
No. Females Scheduled for Cesarean-Section	8	8	8	8	8
Noteworthy Findings					
Mortality (No. of Females)	0	0	0	0	0
Physical Examinations					
Feces, not present	0	0	0	0	[1 (1 day)]
Feces, scant	0	1 (1 day)	1 (1 day)	0	[2 (6 days)]
Body Weights (g) – Mean[f]					
GD 7	1757	1781	1805	1770	1777
GD 9	1778	1780	1815	1776	1784
GD 11	1794	1803	1839	1794	1799
GD 13	1829	1842	1892	1838	[1812]
GD 15	1878	1891	1923	1865	[1838]
GD 17	1905	1913	1942	1894	[1857]
GD 19	1922	1935	1961	1907	[1871]
GD 20	1946	1951	1980	1927	[1888]
GD 24	2002	2004	2035	1952	[1951]
GD 28	2078	2085	2118	2032	[2014]

Sec. 2.6.7.13C Reproductive and Developmental Toxicity Study No.: TT #[redacted]-7064 [Ref. 4.2.3.5.2: TT[redacted]7064FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	60	200	500	1000
Number of Animals					
Total No. of Females[b]	12	12	12	12	12
No. Females Scheduled for Cesarean-Section	8	8	8	8	8
Noteworthy Findings (continued)					
Body Weight Change (g) - Mean					
GD 7 to 20	189	170	175	157	[111]
GD 20 to 28	131	134	138	105	125
GD 7 to 28	321	304	313	262	236
GD 7 to Adj. 28 (adjusted for gravid uterine weight)	42	17	50	24	[-32]
Food Consumption (g) - Mean					
GD 5	90	84	89	87	91
GD 8	96	96	90	87	[83]
GD 13	87	98	91	79	[55]
GD 17	96	100	100	94	[68]
GD 21	92	97	100	97	99
GD 25	96	88	88	95	100
GD 28	94	94	94	96	100
Gross Examination[g]	-	-	-	-	-

Sec. 2.6.7.13C Reproductive and Developmental Toxicity Study No.: TT #[redacted]-7064 [Ref. 4.2.3.5.2: TT[redacted]7064FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	60	200	500	1000
Number of Animals					
Total No. of Females[b]	12	12	12	12	12
No. Females Scheduled for Cesarean-Section	8	8	8	8	8
Noteworthy Findings (continued)					
No. Pregnant Females	8	8	8	8	7
No. Nonpregnant Females	0	0	0	0	1
Reproductive Parameters (mean values)					
No. Examined Live Litters	8	8	8	8	7
No. Corpora lutea/pregnant female	7.1	7.0	6.8	7.1	7.6
No. Implantations/pregnant female	6.0	6.6	6.0	5.8	6.3
% Resorptions/implantations (L.M.)	4.3	2.1	7.1	4.6	2.0
% Dead fetuses/implantations (L.M.)	0.0	0.0	0.0	0.0	0.0
No. Live fetuses/pregnant female	5.8	6.5	5.6	5.5	6.1
% Peri-implantation loss (L.M.)	16.1	5.0	11.3	19.2	18.9
% Postimplantation loss (L.M.)	4.3	2.1	7.1	4.6	2.0
Fetal sex ratios (L.M.)	0.41	0.45	0.52	0.36	0.52
Live Fetal Weights (g)					
Females	33.4	30.6	32.6	29.9	31.3
Males	34.5	31.9	32.7	31.0	30.1

Sec. 2.6.7.13C Reproductive and Developmental Toxicity
Effects on Embryo-Fetal Development

Study No.: TT #[redacted]-7064 [Ref. 4.2.3.5.2: TT[redacted]7064FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control)	60	200	500	1000
Number of Animals					
Total No. of Females[b]	12	12	12	12	12
No. Females Scheduled for Cesarean-Section	8	8	8	8	8
Noteworthy Findings (continued)					
Placental Morphology					
No. abnormal placentas/total examined[e]	0/46	0/52	0/45	0/44	0/43
Fetal Morphology					
External examination	-	-	-	-	
Visceral examination	-	-	-	-	
Coronal examination	-	-	-	-	
Skeletal examination	-	-	-	-	-

– No noteworthy findings; [ ] Test article related change; #/# number affected/number examined.
Fetal sex ratio [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)]
% Peri implantation loss [(No. of corpora lutea no. of implantations)/(no. of corpora lutea)] × 100
% Postimplantation loss [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100
GD Gestation Day; L.M. Litter Mean; MOV Molnupiravir MK 4482 (MK 2801); N/A Not applicable; NR Not reported; TK Toxicokinetics

a GLP compliant with the exception of bioanalytical sample results for NHC, [redacted].
b MOV was detected in plasma from control rabbit #[redacted]0003 at 7 hours following dosing on GD 15. Given the low MOV concentration detected, low incidence, it was confirmed that the animal was not dosed with MOV.
c Due to incorrect plasm sample volumes collected for the 200 mg/kg/day group at 0.5, 1, 2, and 24 hrs postdose, toxicokinetic data for the 200 mg/kg/day dose group are not reported.
d For each group, 8 females were designated for cesarean section and 4 females were designated for toxicokinetic blood collection.
e The toxicokinetic data for NHC was not reported because of lack of reproducibility of the bioanalytical data for this analyte.
f Body weight loss (8% to 9%) occurred in one female assigned to the cesarean section component and in two females assigned to the toxicokinetic component.
g Limited to examination of the thoracic and abdominal viscera.

Sec. 2.6.7.13D Reproductive and Developmental Toxicity (Effects on Embryo-Fetal Development): Report Title: Preliminary Oral Embryo-fetal Developmental Toxicity and Toxicokinetic Study in Rabbits (TT #[redacted]-7010)

Design Similar to ICH 4.1.3? Yes
Species/Strain: Rabbit, Dutch Belted
Age on GD 0: ~28 to 29 weeks
Study Start Date: [redacted]
Special Features: TK - GD 15 (4 females/dose group)

Day of Mating: GD 0
Day of Cesarean-Section: GD 28
Method of Administration: Dosing Volume: 5 mL/kg
Vehicle/Formulation: 1.0 % Methylcellulose in deionized water

Test Article: Molnupiravir
Study Number: TT #[redacted]-7010
Location in CTD: [Ref. 4.2.3.5.2: TT[redacted]7000FIN]
GLP Compliance: Yes[a]

Treatment Interval: GD 7 through 19 (females scheduled for cesarean-section), GD 7 through 15 (females scheduled for TK blood collection)

No-Observed-Effect Level: 125 mg/kg/day (maternal toxicity) and 400 mg/kg/day (developmental toxicity)

No-Observed-Adverse-Effect Level: 125 mg/kg/day (maternal toxicity) and 400 mg/kg/day (developmental toxicity)

Daily Dose (mg/kg/day)	0 (Control)	125	400	750
Maternal Toxicokinetics (GD 15)[b]		**NHC**		
$AUC_{0\text{-}24hr}$ (µM•hr)	NA	111	490	1360
C_{max} (µM)	NA	65.4	204	379
T_{max} (hr)	NA	0.750	1.00	1.13

Sec. 2.6.7.13D Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7010 [Ref. 4.2.3.5.2: TT[redacted]7010FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	125	400	750
Number of Animals				
Total No. of Females[c]	23	23	23	23
No. Females Scheduled for Cesarean-Section	19	19	19	19
Noteworthy Findings				
Mortality (No. of Females)	0	0	0	0
Physical Examinations				
Feces, not present	5 (2 days)	3 (3 days)	2 (1 day)	[3 (2 days)]
Feces, scant	5 (3 days)	6 (2 days)	3 (3 days)	[6 (5 days)]
Feces, unformed	1 (1 day)	2 (3 days)	[3 (4 days)]	[4 (5 days)]
Body Weight Change (g) - Mean				
GD 7 to 20	134	127	[94]	[110]
GD 20 to 28	134	130	[116]	[110]
GD 7 to 28	268	258	[210]	[220]
GD 7 to adj. 28 (adjusted for gravid uterine weight)	-25	-35	[-88]	[-65]

Sec. 2.6.7.13D Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7010 [Ref. 4.2.3.5.2: TT[redacted]7010FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	125	400	750
Number of Animals				
Total No. of Females[c]	23	23	23	23
No. Females Scheduled for Cesarean-Section	19	19	19	19
Noteworthy Findings (continued)				
Food Consumption (g/day) - Mean				
GD 5	74	71	71	76
GD 8	83	83	70	77
GD 13	78	81	[57]	[45]
GD17	88	87	75	70
GD 21	86	80	75	84
GD 25	81	81	80	89
GD 28	84	79	80	87
Gross Examination[d]	-	-	-	-

Sec. 2.6.7.13D Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7010 [Ref. 4.2.3.5.2: TT[redacted]7010FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	125	400	750
Number of Animals				
Total No. of Females[c]	23	23	23	23
No. Females Scheduled for Cesarean-Section	19	19	19	19
No. Pregnant Females	19	19	18	19
No. Nonpregnant Females	0	0	1	0
Noteworthy Findings (continued)				
Reproductive Parameters (mean values)				
No. Examined Live Litters	19	19	18	19
No. Corpora lutea/pregnant female	7.1	7.0	7.4	7.5
No. Implantations/pregnant female	6.4	6.4	6.7	7.0
% Resorptions/implantations (L.M.)	1.4	0.8	0.0	2.8
% Dead fetuses/implantations (L.M.)	0.0	0.0	0.0	0.0
No. Live fetuses/pregnant female	6.3	6.3	6.7	6.8
% Peri-implantation loss (L.M.)	9.3	9.6	9.1	7.5
% Postimplantation loss (L.M.)	1.4	0.8	0.0	2.8
Fetal sex ratios (L.M.)	0.41	0.46	0.50	0.48
Live Fetal Weights (g)				
Females	31.8	32.1	31.2	[29.1]
Males	32.9	33.2	31.3	[29.5]

Sec. 2.6.7.13D Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7010 [Ref. 4.2.3.5.2: TT[redacted]7010FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg/day)	0 (Control)	125	400	750
Number of Animals				
Total No. of Females[c]	23	23	23	23
No. Females Scheduled for Cesarean-Section	19	19	19	19
Noteworthy Findings (continued)				
Placental Morphology				
No. abnormal placentas/total examined	0/120	0/120	0/121	0/129
Fetal Morphology				
External examination	-	-	-	-
Visceral examination	-	-	-	-
Coronal examination	-	-	-	-
Skeletal examination	-	-	-	-

– No noteworthy findings; [ ] Test article related change; #/# number affected/number examined
Fetal sex ratio [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)]
% Peri implantation loss [(No. of corpora lutea no. of implantations)/(no. of corpora lutea)] × 100
% Postimplantation loss [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100
GD Gestation Day; L.M. Litter Mean; N/A Not applicable; NHC N hydroxycytidine (EIDD 1931); TK Toxicokinetics

a GLP [redacted]

b NHC concentrations in plasma from all control group animals were below the lower limit of quantitation.
c For each group, 19 females were designated for cesarean section and 4 females were designated for toxicokinetic blood collection.
d Limited to examination of the thoracic and abdominal viscera.

Sec. 2.6.7.14 Reproductive and Developmental Toxicity (Effects on Pre- and Postnatal Development, Including Maternal Function): Report Title: A Pre- and Postnatal Development Study by Oral (Gavage) in Rats, Including a Postnatal Behavioral/Functional Evaluation (TT #[redacted]-9010)

Test Article: Gefapixant

Design Similar to ICH 4.1.2? Yes
Species/Strain: Rat / Crl:CD(SD)
Initial Age: 59 to 76 days
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing (F_0 generation): GD 6 through LD 20
Day of Mating: GD 0
Method of Administration: Oral (gavage)
Vehicle/Formulation: 1.0% methylcellulose in deionized water
Litters Culled/Not Culled: Culled on PND 4 to 8 pups (4 males, 4 females) when possible; 22 F_1 rats/sex/group (1/sex/litter) were selected on PND 21 for continued evaluation

Study Number: TT #[redacted]-9010
Location in CTD: Vol. Section [Ref. 4.2.3.5.3: TT[redacted]9010FIN]
GLP Compliance: Yes [a]

Special Features: None
No-Observed-Adverse-Effect Level: ≥500 mg/kg/day for maternal toxicity; ≥500 mg/kg/day for F_1 generation toxicity

Daily Dose (mg/kg/day)	0 (Vehicle Control)	100	250	500
Number of Toxicokinetic F_0 Females	8	8	8	8
	MOV			
Toxicokinetics – LD 10				
$AUC_{0\text{-}24\ hr}$ (μM•hr)	N/A [b]	0.190	0.786	1.79
C_{max} (μM)	N/A [b]	0.155	0.569	0.953
T_{max} (hr)	N/A [b]	0.500	0.500	0.500
	NHC			
Toxicokinetics – LD 10				
$AUC_{0\text{-}24\ hr}$ (μM•hr)	N/A [b]	9.12	62.6	122
C_{max} (μM)	N/A [b]	7.67	34.0	75.3
T_{max} (hr)	N/A [b]	0.500	1.00	1.00

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9010 [Ref. 4.2.3.5.3: TT[redacted]9010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg/day)	0 (Vehicle Control)	100	250	500
Number of Main F_0 Females	22	22	22	22
Noteworthy Findings – F_0 Generation				
Mortality	1 [c]	0	0	0
Clinical Observations	-	-	-	-
Body Weight Gain (%) [c]				
GD 15 to 18	40.6 g	-8.9	[-20.0**]	[-19.5**]
GD 18 to 20	31.4 g	-15.3	-6.7	[-16.9*]
GD 6 to 20	128.5 g	-7.9	[-9.8*]	[-13.4**]
Food Consumption	-	-	-	-
Natural Delivery Observations				
No. Females Pregnant	21	19	22	18
Mean Gestation Length (Days)	21.1	21.3	21.3	21.6*
Gestation Index (%)	100	100	100	100
No. Females Completing Delivery	21	19	22	18
No. Females with Liveborn Pups	21	19	22	18
No. Females with no Liveborn Pups	0	0	0	0
No. of Females with Stillborn Pups	3	1	0	1
Mean No. Stillborn Pups/Litter	2.82	0.40	0.00	0.56
No. Pups Stillborn	8	1	0	1

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9010 [Ref. 4.2.3.5.3: TT[redacted]9010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg/day)	0 (Vehicle Control)	100	250	500
Number of Main F_0 Females	22	22	22	22
Noteworthy Findings – F_0 Generation (Continued)				
Mean No. Live Newborn Pups	11.8	11.4	11.9	11.1
Mean Live Birth Index (%)	97.18	99.60	100.00	99.44
Mean Live Male Pups/Litter Birth (%)	51.09	58.19	53.14	48.98
Mean Implantation Sites (Total)	12.9	12.1	12.3	11.7
Mean Post-implant Loss/Litter (%)	5.16	5.89	3.06	4.19
Litter Observations				
Females with Liveborn	21	19	22	18
Mean Viability Index (%)	96.11	99.56	92.86	99.38
Mean Lactation Index	95.24	99.34	98.81	99.31
Mean Live Mall Pups/Litter PND 21 (%)	48.75	54.98	49.49	48.51
Gross Pathology	-	-	-	-
Noteworthy Findings – F_1 Preweaning				
Clinical Observations	-	-	-	-
Pup Body Weights	-	-	-	-
Reflex and Physical Development (eye opening or pinna detachment)	-	-	-	-
Pup Macroscopic Observations	-	-	-	-

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9010 [Ref. 4.2.3.5.3: TT[redacted]9010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg/day)	0 (Vehicle Control)	100	250	500
Noteworthy Findings – F_1 Postweaning				
No. of F_1 Animals (Females/Males)	22/22	22/22	22/22	22/22
Mortality	0/1 [d]	0/0	0/0	0/0
Clinical Observations	-	-	-	-
Body Weights	-	-	-	-
Food Consumption	-	-	-	-
Sexual Maturation				
Males - Preputial Separation	-	-	-	-
Females – Vaginal Patency	-	-	-	-
Behavioral Endpoints				
Motor Activity	-	-	-	-
Acoustic Startle Habituation	-	-	-	-
Morris Water Maze	-	-	-	-
Reproductive Performance				
Group Size – Males	22	22	22	22
Paired Males	21	22	22	22
Mated Males	20	22	22	22
Male Impregnated a Female	20	21	19	18
Male Mating Index (%)	95.2	100.0	100.0	100.0
Male Fertility Index (%)	100.0	95.5	86.4	81.8
Male Pregnancy Index (%)	100.0	95.5	86.4	81.8

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9010 [Ref. 4.2.3.5.3: TT[redacted]9010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg/day)	0 (Vehicle Control)	100	250	500
Noteworthy Findings – F_1 Postweaning (Continued)				
No. of F_1 Animals (Females/Males)	22/22	22/22	22/22	22/22
Group Size - Females	22	22	22	22
Paired Females	22	22	22	22
Mated Females	22	22	22	22
No Females Pregnant	22	21	19	18
Mean Pre-coital Interval (Days)	3.5	2.5	2.4	2.7
Pregnant No. Confirmed Mating	0	0	0	0
Confirmed Mating Days 1 to 7	21	22	22	22
Confirmed Mating Days 8 to 14	0	0	0	0
Confirmed Mating Days 15 to 21	1	0	0	0
Female Mating Index (%)	100.0	100.0	100.0	100.0
Female Fertility Index (%)	100.0	95.5	86.4	81.8
Female Pregnancy Index (%)	100.0	95.5	86.4	81.8
Gross Pathology	-	-	-	-
Reproductive Parameters				
Females with Live Embryos	22	21	19	18
Females with any Nonviable	15	11	5	7
Females with all Nonviable	0	0	0	0

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-9010 [Ref. 4.2.3.5.3: TT[redacted]9010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg/day)	0 (Vehicle Control)	100	250	500
Noteworthy Findings – F_1 Postweaning (Continued)				
Aborted	0	0	0	0
Delivered	0	0	0	0
Mean Number of Corpora Lutea	18.5	17.2	14.7†† e	17.6
Mean Number of Implantations	17.9	16.7	13.8†† e	16.8
Mean Pre-Implantation Loss	3.18	3.49	9.96	3.85
Mean Total No. of Embryos	17.9	16.7	13.8†† e	16.8
Mean Number of Live Embryos	16.8	15.9	13.5	16.3
Mean Number of Dead Embryos	1.0	0.8	0.3† e	0.5
Mean Post-Implant Loss Embryo	5.96	4.62	2.00	3.01

(footnotes presented on following page)

Sec. 2.6.7.14 Reproductive and Developmental Toxicity Study No.: TT #[redacted]-9010 [Ref. 4.2.3.5.3: TT[redacted]9010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

No noteworthy findings; [ ] Test article related change based on incidence and/or severity; * Anova & Dunnett: $p \leq 0.05$; ** Anova & Dunnett: $p \leq 0.01$; † Kruskal Wallis & Dunn: $p \leq 0.05$; †† Kruskal Wallis & Dunn: $p \leq 0.01$; $AUC_{0\text{-}24hr}$ Area under the curve from time 0 to 24 hours; C_{max} Maximum observed concentration; GD Gestation day; GLP Good Laboratory Practice; LD Lactation day; LLOQ Lower limit of quantitation; MOV molnupiravir MK 4482 (EIDD 2801); N/A Not applicable; PND Postnatal day; T_{max} Time of maximum observed concentration

Male Mating Index Mated males/paired males; Male Fertility Index Male impregnated a female/males paired; Male Pregnancy Index Male impregnated a female/mated males; Female Mating Index Mated females/paired females; Female Fertility Index Pregnant females/paired females; Fecundity Index Pregnant females/mated females

a GLP, [redacted].

b MOV and NHC concentrations in plasma from all control group animals at 0.5 hours postdose were below the lower limit of quantitation of the bioanalytical method (<0.00304 µM for MOV; <.0.0193 µM for NHC).

c One F0 generation female was sacrificed due to adverse clinical condition on LD 5. This female had clinical signs including piloerection, pale discolored skin, abnormal gait, labored breathing, uncoordinated gait, and hypothermia and body weight loss between LDs 4 and 5. Necropsy revealed enlarged liver and spleen. All other examined tissues appeared normal.

d One male in the control group was found dead on PND 77. There were no adverse clinical observations or body weight losses noted for this male rat prior to death. Necropsy revealed no gross lesions. A cause of death could not be determined.

e Decreased average numbers of corpora lutea, implantations, total number of embryos, and number of dead embryos in the 250 mg/kg/day group were attributed to three females with small litters (only 1 or 5 embryos) and occurred in a non dose dependent manner. Therefore, they were considered unrelated to maternal administration of MOV.

Sec. 2.6.7.15 Reproductive and Developmental Toxicity (Studies in Which the Offspring (Juvenile Animals) are Dosed and/or Further Evaluated)

Studies in juvenile animals have not been completed.

Sec. 2.6.7.16 Local Tolerance

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Doses	Gender and No. per Group	Noteworthy Findings	Study Number
Isolated bovine corneas	In vitro	0.75 g	5 corneas	MOV was classified as a mild irritant.	TT #[redacted]-7801 [Ref. 4.2.3.6: TT[redacted]78 01FIN]
MatTek EpiDerm™ tissue samples	In vitro	100 mg	Each treatment was conducted in duplicate	MOV was classified as a very mild irritant.	TT #[redacted]-7802 [Ref. 4.2.3.6: TT[redacted]78 02FIN]

MOV Molnupiravir MK 4482 (EIDD 2801)

Sec. 2.6.7.17A Other Toxicity Studies – Immunotoxicity

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Immunotoxicity						
Mouse (CBA-J)	Topical	3 days	Control (DMF), 25% (w/v) MOV, Positive Control (25% HCA)	5F	The sensitivity index (SI) following the 25% test article treatment was 3.2. MOV was considered a dermal sensitizer in this assay.	TT #[redacted]-7803 [Ref. 4.2.3.7.2: T T[redacted]7803FIN]

DMF N,N Dimethylformamide; F Female; HCA hexylcinnamaldehyde; MOV Molnupiravir MK 4482 (EIDD 2801)

Sec. 2.6.7.17B Other Toxicity Studies - Photoreactivity

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Photoreactivity (Reactive Oxygen Species)						
NA	In vitro	NA	200 µM	NA	Both MOV and NHC were shown to not generate ROS, including superoxide anion and singlet oxygen at an aqueous concentration of 200 µM, and are not considered to be photoreactive according to ICH S10, Photosafety Evaluation of Pharmaceuticals guideline.	TT #[redacted]-7814 [Ref. 4.2.3.7.7: TT[redacted]7814FIN]

MOV Molnupiravir MK 4482 (EIDD 2801); NA Not Applicable; NHC=N-hydroxycytidine (EIDD 1931)

Sec. 2.6.7.17C Other Toxicity Studies - Toxicokinetic

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Toxicokinetic Studies						
Mouse/CByB6F1 Tg(HRAS)2Jic	Oral (gavage)	7 days	100, 300, 700, 2000	18/gender/group	There was no mortality and no MOV related changes in clinical observations, body weights, or food consumption. Following daily oral dosing of MOV, no substantial sex differences in plasma NHC $AUC_{0\text{-}24hr}$ and C_{max} values were observed on Study Day 7. Mean plasma NHC $AUC_{0\text{-}24hr}$ and C_{max} values were approximately dose proportional between 100 and 700 mg/kg/day MOV doses, and greater than dose proportional between 700 and 2000 mg/kg/day.	TT #[redacted]-9011 [Ref. 4.2.3.7.7: TT[redacted]9011FIN]

MOV Molnupiravir MK 4482 (EIDD 2801); NHC N hydroxycytidine (EIDD 1931)

Sec. 2.6.7.17C Other Toxicity Studies -Toxicokinetic (Continued)

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Rat/Crl:CD(SD); Rat/Fischer 344: F344/NHsd	Oral (gavage)	5 days	50, 150, 500	11 M/group	There was no MOV related mortality. In male Crl:CD(SD) rats, mean plasma MOV $AUC_{0\text{-}24\ hr}$ values were generally dose proportional between 50 and 150 mg/kg/day, but slightly greater than dose proportional between 150 and 500 mg/kg/day. Mean plasma MOV C_{max} values were greater than dose proportional between 50 and 500 mg/kg/day. Mean plasma NHC $AUC_{0\text{-}24\ hr}$ and C_{max} values were greater than dose proportional between 50 and 500 mg/kg/day. In male F344/NHsd rats, mean plasma MOV and NHC $AUC_{0\text{-}24\ hr}$ and C_{max} values were greater than dose proportional between 50 and 500 mg/kg/day. In male Crl:CD(SD) and F344/NHsd rats, mean plasma NHC $AUC_{0\text{-}24\ hr}$ and C_{max} values were substantially higher than values achieved for MOV (99 to 160 times and 86 to 97 times, respectively, in Crl:CD(SD) rats; and 63 to 80 times and 53 to 89 times, respectively, in F344/NHsd rats). Mean plasma MOV $AUC_{0\text{-}24\ hr}$ and C_{max} values in F344/NHsd rats were generally similar to those achieved in Crl:CD(SD) rats, except at 50 mg/kg/day, when the mean $AUC_{0\text{-}24\ hr}$ value in F344/NHsd rats was slightly lower (0.69 times) than that achieved in Crl:CD(SD) rats. Mean plasma NHC $AUC_{0\text{-}24\ hr}$ values in F344/NHsd rats were generally lower (0.44 to 0.53 times) than those achieved in Crl:CD(SD) rats, and the mean NHC C_{max} value at 50 mg/kg/day in F344/NHsd rats was slightly lower (0.68 times) than that achieved in Crl:CD(SD) rats; however, mean NHC C_{max} values at 150 and 500 mg/kg/day were similar in both rat strains.	TT # [redacted] 1015 [Ref. 4.2.3.7.7: TT [redacted] 1015FIN]

M Male; MOV Molnupiravir MK 4482 (EIDD 2801); NHC N hydroxycytidine (EIDD 1931)

Sec. 2.6.7.17C Other Toxicity Studies -Toxicokinetic (Continued)

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit (Dutch Belted) Nonpregnant	Oral (gavage)	14 days	0, 3, 30, 300, 1000	3 F/group	MOV related effects were limited to mean body weight loss (an average of 36 g between Study Days 1 and 15, compared to +75 g in controls)and unsatisfactory food consumption at 1000 mg/kg/day. Mean plasma MOV $AUC_{0\text{-}24\ hr}$ was not assessed at 3 mg/kg/day because many samples were below the LLOQ. Mean plasma MOV $AUC_{0\text{-}24\ hr}$ values were generally less than dose proportional between 30 and 1000 mg/kg/day; while mean plasma MOV C_{max} values were similar between 3 and 30 mg/kg/day, and generally increased in a dose proportional manner between 30 and 1000 mg/kg/day. Mean plasma NHC $AUC_{0\text{-}24\ hr}$ values were dose proportional between 3 and 30 mg/kg/day doses of MOV, and greater than dose proportional between 30 and 1000 mg/kg/day doses. Mean plasma NHC C_{max} values were dose proportional across all MOV doses.	TT #[redacted] 7043 [Ref. 4.2.3.7.7: TT[redacted] 7043FIN]

F Female; LLOQ Lower limit of quantitation; MOV Molnupiravir MK 4482 (EIDD 2801); NHC N hydroxycytidine (EIDD 1931)

Sec. 2.6.7.17C Other Toxicity Studies -Toxicokinetic (Continued)

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Dog/beagle	Ora (gavage)	16 days	6 (QD), 17 (Q3D)	3F at 6 (QD); 3M at 17 (Q3D)	No MOV related mortality or changes in hematology. After repeated oral dosing of MOV, mean plasma MOV and NHC $AUC_{0\text{-}24hr}$ (6 mg/kg/day), $AUC_{0\text{-}72hr}$ (17 mg/kg/Q3D) and C_{max} values were similar to those achieved on Study Day 1, demonstrating that steady state exposures were generally achieved following the first dose, with no apparent accumulation or loss of exposure after repeated dosing. Mean plasma NHC $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}72hr}$ and C_{max} values were approximately 15 to 34 times those achieved after respective dosing for MOV. NHC TP was detected in PBMCs after MOV dosing at 6 mg/kg/day and 17 mg/kg/Q3D. Highest PBMC NHC TP concentrations were observed at 2 hours post MOV dosing for both dosing regimens. At 6 mg/kg/day, mean NHC TP concentrations in PBMCs were less than 2 fold higher on Study Day 16 than those attained on Study Day 1. At 17 mg/kg/Q3D, mean PBMC NHC TP concentrations on Study Day 16 were generally similar to those achieved on Study Day 1. Mean PBMC NHC TP concentrations following 17 mg/kg/Q3D were generally similar (i.e., within 2 fold) to those achieved at 6 mg/kg/day at respective times.	TT #[redacted] 1005 [Ref. 4.2.3.7.7: TT[redacted] 1005FIN]

F Female; M Male; MOV Molnupiravir MK 4482 EIDD 2801; NHC N hydroxycytidine (EIDD 1931); NHC TP N hydroxycytidine 5′ triphosphate (EIDD 2061); PBMC Peripheral blood mononuclear cell; QD Once daily; Q3D Once every 3 days; SD Sprague Dawley; TK Toxicokinetics.

Sec. 2.6.7.17D Other Toxicity Studies – Other

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Rat/Fischer 344: F344/NHsd	Oral (gavage)	7 days	0, 250, 500	3 males/group	No mortality was noted. All animals survived until the end of the assay. Ruffled fur was observed in all animals at 250 and 500 mg/kg/day beginning on Study Day 5 and hunched posture was seen in one animal at 500 mg/kg/day beginning on Study Day 6. There were no notable changes in food consumption and body weight. Compared to controls, there were very slight, statistically significantly, decreases in mean RBC, HGB, and HCT at 250 mg/kg/day (10% to 12%) and 500 mg/kg/day (16 to 17%) on Day 8. These changes may represent test article related effects but it should be noted that the greater blood volume collected from these groups (and not from controls) on Day 7 for bioanalysis likely contributed to these lower values. Rats were exposed to NHC at both doses (Study Day 7 $AUC_{0\text{-}24hr}$ of 133 µM*hr and 233 µM*hr at 250 and 500 mg/kg/day, respectively). Based on results of this study, MOV at concentrations up to 500 mg/kg/day was tolerated for 7 days of dosing in male Fischer 344 rats.	TT #[redacted] 9027 [Ref. 4.2.3.7.7: TT[redacted] 9027FIN]

HCT Hematocrit; HGB Hemoglobin; MOV Molnupiravir MK 4482 (EIDD 2801); NHC N hydroxycytidine (EIDD 1931); RBC Red Blood Cells

Sec. 2.6.7.17D Other Toxicity Studies – Other (Continued)

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Other Studies (continued)						
Rat/transgenic Fischer 344 Big Blue®	Oral (gavage)	28 days	0, 50, 150, 500 Positive Control (20)	6 males/ dose group	The supporting Big Blue® mutation analysis portion of the study was not conducted based on the negative results in somatic cells, liver and bone marrow in another study in Big Blue® transgenic F344 rats (TT # [redacted] 9025); therefore, only in life results are presented below. There were no unscheduled deaths. One animal in the 50 mg/kg/day group was replaced on Day 1 due to high body weight loss. Ruffled fur and piloerection were observed in animals in all test and control article dose groups. Hypersalivation was also observed in two animals at 500 mg/kg/day, while red nasal discharge was observed in one animal each in the 150 mg/kg/day and positive control dose groups. A decrease in mean body weight gain was noted at 500 mg/kg/day (12% difference compared to the vehicle control group). There were no notable changes in food consumption.	TT # [redacted] 9047 [Ref. 4.2.3.7.7: TT [redacted] 9047FIN]

Sec. 2.6.7.17D Other Toxicity Studies – Other (Continued)

Test Article: Molnupiravir

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group [a]	Noteworthy Findings	Study Number
Monkey (rhesus)	Oral (gavage)	7 consecutive days/dose	150, 300, 500	3 males, 3 females	In this tolerability study, administration of MOV at doses up to 500 mg/kg/day was well tolerated, with no test article related mortality, or changes in body weight, food consumption, or clinical pathology parameters. MOV related clinical observations of nonformed and/or liquid feces in males administered ≥300 mg/kg/day and females administered 300 mg/kg/day were considered nonadverse. Thus, no dose level exceeded the MTD. Plasma concentrations of MOV were quantifiable in all animals at 0.5 hours postdose, indicating that MOV was readily absorbed following single and multiple oral doses. However, no meaningful TK parameters could be established for MOV due to very low systemic exposure. Plasma concentrations of NHC were quantifiable in all animals at 0.5 hours postdose, indicating NHC was readily formed following single and multiple oral doses of MOV. Following a single oral dose of 150, 300, or 500 mg/kg/day of MOV, exposure (according to C_{max} and AUC_{inf}) to NHC generally increased. Following multiple oral doses of 150, 300, or 500 mg/kg/day, little to no systemic accumulation of NHC was observed. Peak and total exposures to NHC were generally similar (<2 fold difference) in males and females.	TT #[redacted] 7817 [Ref. 4.2.3.7.7: TT[redacted] 7817FIN]

MOV Molnupiravir MK 4482 (EIDD 2801); MTD Maximum Tolerated Dose; TK Toxicokinetic

a The same animals were used for each dose in the 7-day monkey tolerability study, with a 7-day washout period between doses (TT #[redacted]-7817).