MORPHIC THERAPEUTIC

ABSTRACT # P037

Nonclinical Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion Properties of MORF-057 Support its Clinical Development as an Oral Selective $\alpha_4\beta_7$ Integrin Inhibitor

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Background

MORF-057 is a potent and selective oral small molecule inhibitor of the $\alpha_4\beta_7$ integrin that is being assessed in a Phase 1 clinical study for safety, pharmacokinetics (PK), and pharmacodynamics. Previous studies demonstrated MORF-057-mediated inhibition of T cell gut homing in a mouse model, and an increase in $\alpha_4\beta_7$ High central memory T cells in monkeys (Wong et al., DDW 2020, Redhu et al., AAI 2021). Using a receptor occupancy (RO) assay under physiologically relevant conditions, MORF-057 achieves 90% $\alpha_4\beta_7$ RO at approximately 10 nM in human whole blood (Mangada et al., UEG 2020). The current studies evaluate nonclinical pharmacokinetics and properties of absorption, distribution, metabolism, and excretion (ADME) to enable dose/exposure projection to humans.

METHODS

PK studies were conducted in mouse, rat, dog, and monkey following intravenous (IV) and oral administration. ADME studies were conducted in vitro and in rats using a single dose of 10 mg/kg carbon-14 [^{14}C] labeled MORF-057. MORF-057 levels were quantified using liquid chromatography coupled with tandem mass spectrometry. Human PK was predicted based on body weight allometry, well-stirred and semi-physiological models. Briefly, cross-species regression using body weight allometry was applied to predict human clearance (CL). Volume of distribution at steady state (Vd_{ss}) was estimated using a combination of allometry and tissue composition models such as Øie-Tozer models. Normalized preclinical PK profiles were then scaled to human PK with the human CL and Vd_{ss} estimates and the PK model parameters for two- and three-compartment PK models were fitted to capture the predicted human PK profile with a 1 mg/kg IV administration.

Results

MORF-057 exhibited low to moderate clearance (CL) in animals with species-dependent volume of distribution (Vd_{ss}) resulting in half-lives of 1.1 to 2.7 hours (Table 1). Following an oral dose, absorption was high with bioavailability ranging from 15% to 49%. MORF-057 is highly protein bound across species (> 98%).

Table 1. MORF-057 PK parameters following IV and oral dosing across species

Species	PPB* (% Free)	IV/P.O. Dose (mg/kg)	CL_p^ (mL/min/kg)	Vd_{ss}^ (L.kg)	$T_{1/2}$^ (hr)	F# (%)
Mouse	0.9	1/10	32.5 (45%)	2.4 (8%)	1.3 (47%)	15
Rat	1.3	1/7.5	23.7 (22%)	3.0 (30%)	2.7 (41%)	39
Dog	0.6	1/5	7.0 (17%)	0.4 (13%)	1.1 (8%)	49
Monkey	0.9	1/5	9.5 (15%)	0.3 (6%)	1.1 (6%)	10

*Plasma protein binding; Human is 1.0% free. ^Mean (CV%) values following IV dose. #Oral bioavailability from dose normalized mean AUC. Abbreviations: AUC: area under the concentration vs time curve; CL_p: plasma clearance; F: bioavailability; P.O.: per os, oral administration; $T_{1/2}$: half-life; Vd_{ss}: volume of distribution at steady state.

Following a single oral dose of [^{14}C]-MORF-057 to Long Evans and to Sprague Dawley rats, distribution of radioactivity in rat was predominantly in the small intestine wall, liver, and stomach wall (Figure 1). Elimination of total radioactivity was rapid with a half-life of approximately 2 hours suggesting a low risk of accumulation following multiple dosing.

[^{14}C]-MORF-057-derived radioactivity was not present in the pigmented tissues (uveal tract and pigmented skin), suggesting a low affinity to the melanin-containing tissues and a low risk of phototoxicity. In addition, [^{14}C]-MORF-057-derived radioactivity was not present in the brain suggesting a low risk of central nervous system distribution. MORF-057 was identified as the predominant circulating species in rat plasma following a single oral dose of [^{14}C]-MORF-057 (Figure 2). Several metabolites of MORF-057 were detected at a low level in rat plasma (data not shown).

Figure 1. Whole body autoradioluminogram showing tissue distribution of radioactivity at 2 hours post-dose following a single oral dose of [^{14}C]-MORF-057 to Long Evans rats at 10 mg/kg

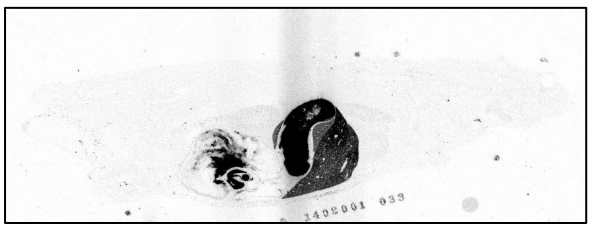
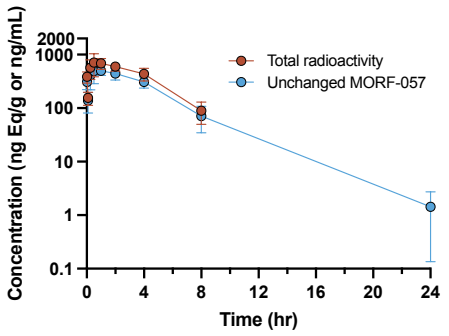


Figure 2. Mean (± Std. Dev.) total radioactivity and unchanged MORF-057 versus time plot in plasma following a single oral dose of [^{14}C]-MORF-057 in Sprague Dawley rats



In order to investigate the relative contribution of liver uptake and metabolism to MORF-057 clearance, monkeys were administered a pre-treatment with rifampin (an OATP1B inhibitor, 20 mg/kg P.O., Shen 2013) or 1-aminobenzotriazole (ABT, a pan-CYP inhibitor, 20 mg/kg P.O.) prior to IV administration of MORF-057 (0.3 mg/kg). Rifampin decreased MORF-057 clearance by 3-fold in monkeys suggesting MORF-057 elimination involves hepatic uptake transport (Figure 3 and Table 2). In addition, ABT decreased clearance by 1.5-fold in monkeys suggesting that MORF-057 is further cleared via CYP3A metabolism followed by biliary/fecal elimination of metabolites (data not shown).

Figure 3. Mean (± Std. Dev.) MORF-057 plasma concentration versus time plots after intravenous infusion (0.3 mg/kg) MORF-057 in non-naïve male Cynomolgus Monkeys

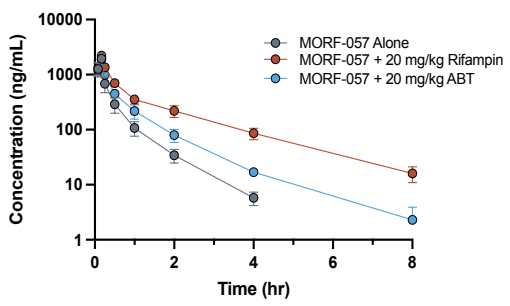


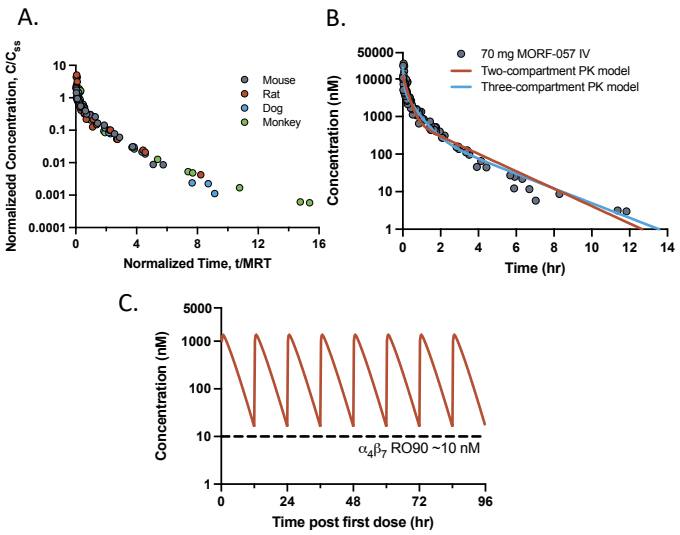
Table 2. MORF-057 PK parameters following IV administration alone or following oral pre-treatment with either rifampin or ABT in Cynomolgus monkeys

Dose (mg/kg)	Treatment Group	$AUC_{0-\infty}$ (µg*hr/mL)	CL_p (mL/min/kg)	Vd_{ss} (L/kg)	$T_{1/2}$ (hr)
0.3	MORF-057 Alone	0.635 (21%)	8.14 (24%)	0.228 (15%)	0.72 (4%)
0.3	MORF-057 + Rifampin	1.71 (17%)	2.99 (16%)	0.278 (13%)	1.6 (7%)
0.3	MORF-057 + ABT	0.932 (3%)	5.37 (3%)	0.267 (17%)	1.2 (25%)

Values shown are the mean and (%CV) from n=3 animals. Abbreviations: ABT= 1-aminobenzotriazole; $AUC_{0-\infty}$ = area under the concentration-time curve from hour 0 to infinity; CLp = plasma total body clearance; IV = intravenous; $T_{1/2}$ = half-life; Vd_{ss} = volume of distribution at steady state.

MORF-057 is predicted to have moderate bioavailability (40%) and CL (6.5 mL/min/kg) in humans. Wajima transformation (Wajima et al. 2004) shows good agreement of the normalized PK across animal species, with a predicted human concentration-time profile supporting >90% $\alpha_4\beta_7$ RO at trough following 200 mg twice daily dose (Figure 4).

Figure 4. MORF-057 animal IV PK following Wajima transformation (A), predicted human PK of MORF-057 after 70 mg single IV dose (B), and projected MORF-057 human PK following 200 mg twice daily oral dose (C).



CONCLUSION/SUMMARY

- These data demonstrate that MORF-057 is well absorbed and its PK/ADME properties in animals support the potential for achieving high $\alpha_4\beta_7$ RO following oral administration in humans.
- These nonclinical results provided a basis for the progression of MORF-057 into a first-in-human Phase 1 clinical study assessing safety, pharmacokinetics, and receptor occupancy (results being reported separately; Ray et al., ECCO 2021).

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