MORPHIC

ABSTRACT # E0359

Full Target Engagement with Saturation of $\alpha_4\beta_7$ Integrin Receptor Occupancy Resulting in Changes in Subset of Lymphocytes by MORF-057 Following 200 mg Twice Daily Dosing in Healthy Subjects

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INTRODUCTION

- MORF-057 is an $\alpha_4\beta_7$ selective integrin inhibitor being developed as an oral treatment for patients with inflammatory bowel disease.
- In a previous Phase 1 study, MORF-057 demonstrated favorable safety, pharmacokinetics (PK) and pharmacodynamic (PD) properties and was well tolerated in healthy subjects dosed up to 100 mg twice daily (BID).[1]
- Aim: To evaluate safety, PK, and PD of an immediate release (IR) formulation in capsule strengths of 25 and 100 mg in doses up to 200 mg BID.

METHODS

- Immediate release formulation in capsules at dosage strengths of 25 and 100 mg.
- Two-part healthy volunteer study.
- Part 1 (n=8): safety and PK of a single administration of 25 mg (fasted) and 100 mg (fasted, fed) MORF-057.
- Part 2 (n=12): safety, PK, and PD of a single dose of 200 mg MORF-057 followed, after washout, by 14 days of repeat dosing at 200 mg BID.
- Blood samples to assess PK (Part 1 and 2) and receptor occupancy (RO; Part 2 only) of $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins were obtained prior to the first dose and 12 hours post-dose.
- Changes in lymphocyte subsets (LS) and expression of C-C Motif Chemokine Receptor 9 (CCR9) mRNA in blood were measured (Part 2).[2]

RESULTS

Pharmacokinetics

- Following oral doses from 25 to 200 mg, approximately dose-proportional systemic exposures of MORF-057 were observed (Figure 1; Table 1).
- MORF-057 was rapidly absorbed with a T_{max} ranging from 2-4 hours.
- The high fat meal delayed the absorption resulting in a slight decrease in AUC (23%) and C_{max} (49%) and an increase in C_{12} (46%) at the 100 mg dose.
- The reduction in MORF-057 exposure following a high fat meal has a minimal impact on the potential clinical effect of MORF-057 given the increase of C_{12}.

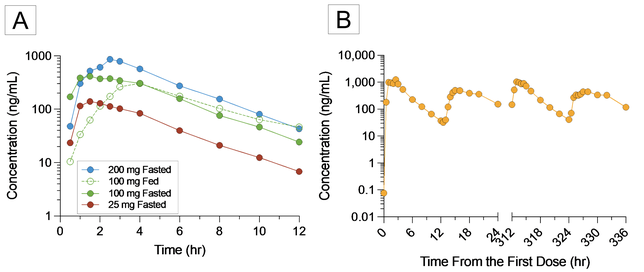

Figure 1. Mean Plasma Concentration of MORF-057 vs. Time Following Single Dose (A) and Twice Daily Dosing at 200 mg (B)

Pharmacokinetic Parameter (Unit)	100 mg MORF-057 (Fasted) (N=8)	100 mg MORF-057 (Fed) (N=7)	25 mg MORF-057 (Fasted) (N=7)	200 mg MORF-057 (Fasted) (N=9)
$AUC_{0\text{-inf}}$ (hr*ng/mL)	2050 (51.2)	1660 (41.1)	604 (36.5)	3770 (30.3)
C_{max} (ng/mL)	545 (45.9)	299 (48.7)	139 (38.6)	970 (46.6)
C_{12} (ng/mL)	19.0 (81.9)	35.1 (98.6)	5.98 (61.8)	40.0 (44.1)
T_{max} (hr)	2.01 (1.02, 4.02)	4.00 (1.50, 4.00)	1.50 (1.00, 2.50)	2.50 (1.52, 4.02)

Table 1. Summary of Plasma MORF-057 PK Parameters Following Single Dose Administration. $AUC_{0\text{-inf}}$, C_{max}, and C_{12} values are presented as geometric mean (geometric CV%). T_{max} is presented as median (min, max).

RO and Pharmacodynamics

- $\alpha_4\beta_7$ RO saturation (≥99%), measured at C_{trough}, was achieved in the 200 mg BID cohort at 12 hours across study days (Figure 2A).
- Combining data with a previous study,[1] a sigmoidal Emax model relating MORF-057 plasma concentration to $\alpha_4\beta_7$ RO showed ≥90% RO was achieved at approximately 8 ng/mL (Figure 2B).

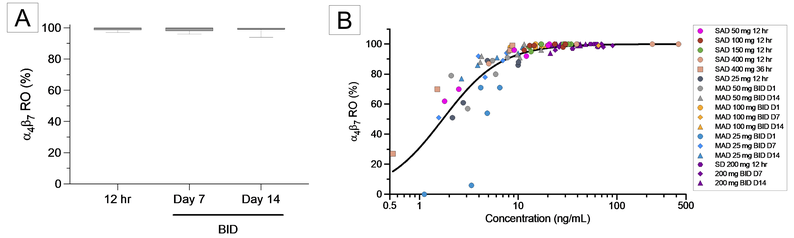

Figure 2. $\alpha_4\beta_7$ RO in a Single Dose of 200 mg and Repeated 200 mg BID Dosing (A) and $\alpha_4\beta_7$ RO vs. MORF-057 Plasma Concentration and Dose (B)

- Selective increases in β_7 expressing effector memory T cells, central memory T cells, switched memory B cells, and CCR9 mRNA in blood were observed on day 14 at MORF-057 doses of 100 and 200 mg BID (Figure 3).
- No significant difference in cell population or CCR9 expression was observed between 100 and 200 mg BID doses. Changes in lymphocyte subsets and CCR9 transcript are consistent with previously reported data.[1] $\alpha_4\beta_1$ RO was below the limit of quantitation with mean trough values estimated to be <5% at 200 mg BID.

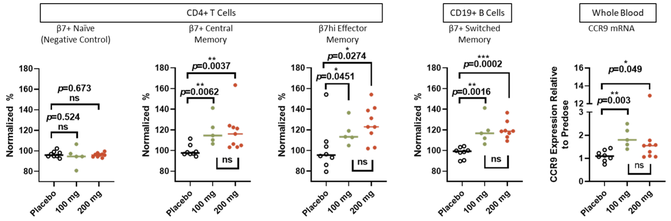

Figure 3. Changes in Pharmacodynamic Biomarkers. Healthy volunteers were treated with the 100 mg BID (n=5)[1,2] and 200 mg BID (n=9) MORF-057 for 14 days; Placebo: n=8. Lymphocyte subset populations were measured at day 14 using multi-color flow cytometry.[2] CCR9 was measured using qRT-PCR. Mann-Whitney U test was used for statistical analysis. β_7 hi=expressing high levels of integrin β_7; β_7+=expressing β_7.

Safety

- A total of 20 subjects were enrolled in the study (n=8 in Part 1; n=12 in Part 2).
- Three non-serious adverse events were reported.
- No adverse events were deemed related to MORF-057.
- No safety signals were identified.

CONCLUSIONS

- Single and multiple doses of MORF-057 at up to 200 mg BID for 14 days were well tolerated.
- PK and food effect of the 25 mg and 100 mg IR capsule are comparable to those observed in a previous study.[1]
- Consistent with C_{trough} $\alpha_4\beta_7$ RO saturation at both 100 and 200 mg BID, similar biomarker responses were observed with 14 days of BID dosing at the two dose levels suggesting saturation of biomarker effect at doses at or above 100 mg BID at this timepoint.
- MORF-057 demonstrated a favorable safety, PK, and PD profile supporting further clinical development.

Disclosures

- All authors were employed by Morphic Therapeutic for the duration of the study.
- A. Chavan, J. Jones, M. Chae, L. JeBailey and A.S. Ray are past employees of Morphic Therapeutic.

Acknowledgments

- All members of the MORF-057 discovery and development team.

Contact

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References

1. Ray A et al. P306 ECCO, 2021.
2. Hussain A et al. P0417 UEG, 2022.