ABSTRACT # P306

MORF-057, an Oral Selective $\alpha_4\beta_7$ Integrin Inhibitor for Inflammatory Bowel Disease, Leads to Specific Target Engagement in a Single and Multiple Ascending Dose Study in Healthy Subjects

A Ray, D Cui, D Lee, M M Mangada, J Jones, G Bain, P G Traber, L H Vrishabhendra, P W Krzeski, N Vande Casteele, M M Reardon, T P Stern, C L Soo, H Nguyen, B N Rogers, P G Linde

BACKGROUND

MORF-057, an oral small molecule designed to selectively inhibit integrin $\alpha_4\beta_7$, is being studied as a therapy for inflammatory bowel disease (IBD). Inhibition of $\alpha_4\beta_7$ is a validated mechanism for the treatment of IBD as demonstrated by vedolizumab (Entyvio®), a monoclonal antibody. MORF-057 is orally administered and avoids the need for periodic therapeutic infusions. This study evaluated single (SAD), multiple ascending doses (MAD), and food effect (FE) of MORF-057 in healthy subjects.

METHODS

This was a randomized, double-blind, placebo-controlled, single and multiple dose phase 1 study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of MORF-057 conducted in a Phase 1 Unit in the USA (NCT04580745). Healthy subjects were randomized 3:1 to receive a single dose of MORF-057 at 25, 50, 100, 150, and 400 mg or matching placebo in the SAD cohorts; or twice daily (BID) doses of 25, 50, and 100 mg MORF-057 or matching placebo for a total of 14 days in the MAD cohorts. Pre-dose and post-dose trough PK samples were obtained to assess MORF-057 exposure and PK parameters. Blood samples were collected to assess receptor occupancy (RO) of $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins before the first dose, and 12 hours post-dose in the SAD cohorts and in the MAD cohorts on Days 1, 7, and 14. Peripheral blood mononuclear cells (PBMC) and whole blood RNA were obtained to evaluate the PD biomarkers (lymphocyte subsets and C-C Motif Chemokine Receptor 9 [CCR9], respectively). In addition, FE on MORF-057 PK was evaluated using the selected dose (100 mg) based on data from the SAD cohorts.

RESULTS

Subject Disposition

A total of 67 eligible healthy subjects who met all entry criteria were enrolled into the study; all subjects were randomized and received MORF-057 or placebo, with 36 in the SAD, 9 in the FE, and 22 in the MAD cohorts. Sixty-six completed study treatment and 1 from the 50 mg BID MAD cohort withdrew consent.

Demographic and Baseline Characteristics

Overall, the demographic and baseline characteristics (Table 1) were similar across all cohorts.

Table 1. Demographic and Baseline Characteristics

Demographic/ Baseline Characteristic	SAD Placebo (N=9)	SAD MORF-057 (N=27)	MAD Placebo (N=6)	MAD MORF-057 (N= 16)	FE MORF-057 (N=9)
Age (years)					
Median (min, max)	38.0 (23, 59)	48.0 (21, 61)	48.0 (29, 61)	44.0 (30.0, 64.0)	52.75 (28, 61)
Sex - n (%)					
Female	2 (22.2)	11 (40.7)	1 (16.7)	4 (25.0)	4 (44.4)
Male	7 (77.8)	16 (59.2)	5 (83.3)	12 (75.0)	5 (55.6)
Race - n (%)					
Black or African American	3 (33.3)	10 (37.0)	4 (66.7)	10 (62.5)	4 (44.4)
White	5 (55.6)	17 (62.9)	2 (33.3)	5 (31.25)	5 (55.6)
Multiple	1 (11.1)	0 (0.0)	0 (0.0)	1 (6.25)	0 (0.0)
Ethnicity - n (%)					
Hispanic or Latino	0 (0.0)	1 (3.7)	0 (0.0)	1 (6.3)	0 (0.0)
Not Hispanic or Latino	9 (100.0)	26 (96.3)	6 (100.0)	15 (93.75)	9 (100.0)
BMI (kg/m²)					
Median (min, max)	25.80 (21.9, 31.0)	27.3 (19.1, 31.9)	29.50 (26.8, 31.2)	27.2 (21.7, 31.6)	26.98 (24.5, 31.8)

Pharmacokinetics

Following dosing, MORF-057 was rapidly absorbed, and systemic exposure increased approximately dose-proportionally (Figure 1; Table 2). A slight reduction in peak and total MORF-057 exposure was observed following administration of a single dose of 100 mg in the fed compared to the fasted condition (Figure 1A). The reduction in MORF-057 exposure is not expected to impact the potential clinical effect of MORF-057 following BID dosing as C_{12} values were similar under fed and fasted conditions (Figure 1A).

Figure 1. Mean Plasma Concentration of MORF-057 vs Time in the Food Effect and MAD Cohorts

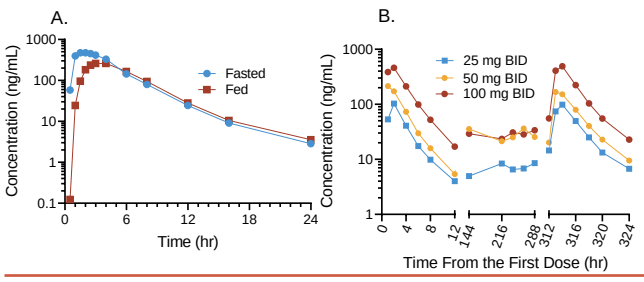


Table 2. Summary of MORF-057 Plasma PK Parameters

	MAD Cohort 25 mg BID		MAD Cohort 50 mg BID		MAD Cohort 100 mg BID	
Parameter[1]	**Day 1**	**Day 14**	**Day 1**	**Day 14**	**Day 1**	**Day 14**
C_{max} (ng/mL)	83.3 (75.7%)	85.8 (63.4%)	184 (81.4%)	143 (89.5%)	466 (30.8%)	519 (13.3%)
AUC[2] (hr*ng/mL)	302 (57.3%)	369 (61.6%)	639 (54.3%)	630 (60.1%)	1735 (36.7%)	1951 (13.5%)
C_{12} (ng/mL)	3.46 (76.1%)	5.88 (66.9%)	4.86 (57.8%)	8.4 (62.3%)	15.7 (47.6%)	22 (28.7%)

1. All PK parameters are reported as geometric mean (geometric CV%).
2. AUC is presented as AUC0-INF for the FE cohort and AUC0-12 for the MAD cohorts.

Receptor Occupancy and Pharmacodynamic Biomarkers

RO increased with dose and study day, achieving saturation (>99%) in individuals in each cohort above 25 mg (Figure 2B and C). A sigmoid E_{max} model relating MORF-057 plasma concentration to $\alpha_4\beta_7$ RO showed ≥90% RO was achieved at approximately 8 ng/mL MORF-057 (Figure 2A). At 100 mg BID of MORF-057 on Day 14, selective increases in β_7 expressing effector memory T cells, central memory T cells, CD3- CD4- lymphocytes (includes B and NK cells) and CCR9 mRNA in blood were observed (Figure 3A and B). A dose- and time-dependent change in β_7 expressing effector and central memory T cells was observed (Figure 3C and D). Changes in lymphocyte subsets and CCR9 transcript are consistent with those reported with other integrin pathway inhibitors including vedolizumab (*Uzzan et al. 2018, Boden et al. 2018, Veny et al. 2021*). $\alpha_4\beta_1$ RO was below the limit of quantitation with mean trough values estimated to be <10% at any of the dose levels.

Figure 2. $\alpha_4\beta_7$ RO vs. MORF-057 Plasma Concentration and Dose

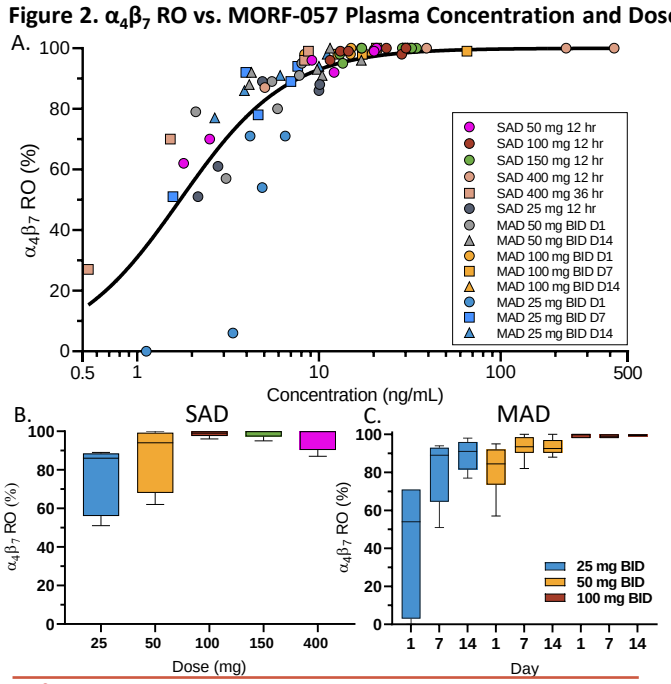
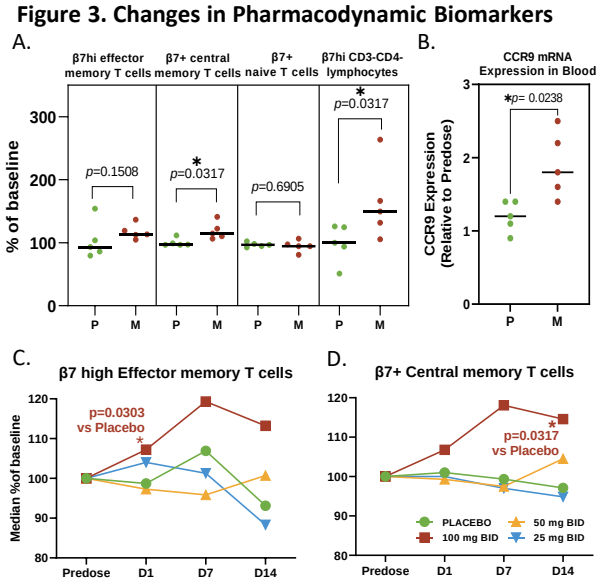


Figure 3. Changes in Pharmacodynamic Biomarkers



Lymphocyte subset populations were measured using multi-color flow cytometry. Mann-Whitney U test was used for statistical analysis. Median is of 5-6 individual data points per treatment and timepoint. β7 high=expressing high levels of integrin β7; β7+=expressing β7; P=placebo; M=MORF-057; D=day

Safety

Overall, there were no safety signals observed in this study. Across the SAD and MAD cohorts, a total of 18 treatment emergent adverse events (TEAEs) from 14 subjects were reported, regardless of causality. Of those, 6 TEAEs from 5 subjects were from the SAD cohort and 12 TEAEs from 9 subjects were from the MAD cohort. All TEAEs were grade 1 except 1 accidental thermal burn (grade 2) (Table 3). Two grade 1 TEAEs were possibly related to study drug: 1 (maculopapular rash) in the MAD placebo cohort and 1 (macular rash) in the MAD MORF-057 100 mg BID cohort. Both cases resolved while subjects remained on study drug without interruption. No serious TEAEs or deaths were reported during the study.

Table 3. Summary of Adverse Events in MAD Cohort by Preferred Terms and Grade

	MAD Placebo (N=6)		MAD MORF-057 (N=16)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any	2 (0.33)	0 (0.0)	10 (0.62)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	2 (0.12)	0 (0.0)
Dry eye	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Ligament sprain	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Rash macular	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Rash maculo-papular	1 (0.17)	0 (0.0)	0 (0.0)	0 (0.0)
Thermal burn	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Vessel puncture site swelling	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Vulvovaginal discomfort	0 (0.0)	0 (0.0)	1 (0.06)	0 (0.0)
Xeroderma	1 (0.17)	0 (0.0)	0 (0.0)	0 (0.0)

CONCLUSIONS

- Single and multiple ascending doses of MORF-057 were well tolerated. No safety signals were identified
- MORF-057 demonstrated a favorable PK profile, where target engagement was confirmed, and a clear PK/PD relationship was established
- A PD signature consistent with that observed with other pathway inhibitors, establishes proof of biological effects resulting from saturating RO
- Results from administration with a high fat meal suggest MORF-057 can be taken without regard to food
- Study results support further investigation of MORF-057 and provide a basis for future dose selection in planned phase 2 studies in patients with IBD

Disclosures: M M Reardon and T P Stern are consultants of Morphic Therapeutic; P Traber is a consultant and a shareholder of Morphic Therapeutic; N Vande Casteele received consultant fee from Morphic Therapeutic; L H Vrishabhendra and P W Krzeski have no relevant disclosures; all other authors are employees and shareholders of Morphic Therapeutic.

Acknowledgements: All members of the MORF-057 Discovery and Development Teams.

Contact: adrian.ray@morphictx.com; peter.linde@morphictx.com