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Increase in Circulating T and B Lymphocyte Subsets After Treatment with the Potent, Selective, Oral Small Molecule α4β7 Inhibitor MORF-057 In Healthy Subjects

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INTRODUCTION

The expanding role of small molecule drugs in modulating the immune system provides innovative opportunities to target autoimmune diseases. Inflammatory bowel disease (IBD) patients experiencing chronic inflammation in their gut have benefited from biologics targeting the α4β7/MAdCAM-1 axis. Integrin heterodimer α4β7 is expressed on a subset of lymphocytes, mediating their extravasation upon binding to the corresponding gut-specific ligand MAdCAM-1. Inhibiting this interaction blocks lymphocytes from infiltrating into the intestinal lamina propria, leading to measurable increases in their circulating levels.[1,2,3] In this study, we explore target engagement and lymphocyte trafficking as pharmacodynamic (PD) readouts in healthy subjects treated with MORF-057, an orally administered small molecule inhibitor of α4β7.

METHODS

Lymphocyte Subsets and Gating Strategy

Two randomized, double-blinded, placebo (PBO)-controlled clinical studies in healthy subjects have been performed to assess safety, tolerability and pharmacokinetics (PK) of MORF-057[2,4]. Here, we characterize changes in lymphocyte subsets during MORF-057 treatment. Blood was collected to assess PK/PD over 14 days. Changes in α4β7 receptor occupancy (RO) and lymphocyte trafficking were explored using flow cytometry on days 0 (pre-treatment/ baseline), 1, 7, and 14. α4β7 RO was measured in whole blood using a MAdCAM-based probe in manganese-free conditions.

Peripheral blood mononuclear cells (PBMC) were isolated, cryopreserved, and used to quantify CD4+ naïve, CD4+ central memory (T_{CM}), CD4+ effector memory (T_{EM}) T cells, and switched memory B cells (B_{SM}) (Table 1).

T Cell Subsets	Markers
CD4+ β7+ Naïve	CD3+CD4+CD45RO-CD27+ β7+
CD4+ β7+ CM	CD3+CD4+CD45RO+CD27+β7+
CD4+ β7 High EM	CD3+CD4+CD45RO+CD27- β7 Hi
B Cell Subsets	**Markers**
CD19+ β7+ Naïve	CD19+CD27-IgD+ β7+
CD19+ β7+ SM	CD19+CD27+IgD- β7+

Table 1. Marker panel for lymphocyte subsets in the study.

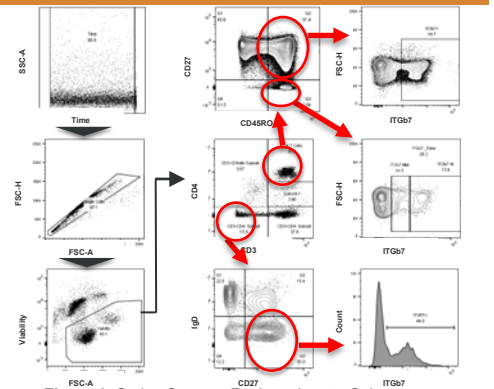

Figure 1. Gating Strategy For Lymphocyte Subsets.

RESULTS

Changes in PD markers vs PBO

T CELLS: Subjects receiving MORF-057 at the two highest doses of 100 and 200 mg BID had a significant increase in both their circulating levels of ITGβ7+ CD4+ T_{CM} cells and ITGβ7 Hi CD4+ T_{EM} cells by day 14 when compared to PBO (Figure 2). No significant changes in naïve T cells were observed in any of the treatment groups. B CELLS: The percent change of ITGβ7+CD19+ B_{SM} cells from baseline was significantly greater for all dose groups compared to PBO (Table 2).

Time dependent increases in PD markers

Increasing trends from baseline to day 14 were observed for the 100 and 200 mg cohorts in all lymphocyte subset populations. Significant differences, relative to baseline, were calculated with the 200 mg cohort at day 1 for the B_{SM} population and day 14 for all populations (Figure 3).

	Pooled Placebo (n=8)	25 mg BID (n=5)	50 mg BID (n=6)	100 mg BID (n=5)	200 mg BID (n=9)
CD4+ memory T cells trough % RO	0	89	94	>99 §	>99
Lymphocyte Subsets (% Change from Baseline)					
CD4+ β7+ central memory T cells	97.7	94.8	104.5	**114.6** **	**116.2** **
CD4+ β7high effector memory T cells	95.5	88.3	100.7	**113.2** *	**122.9** *
β7+ switched memory B cells	99.2	**103.2***	**105.0** *	**116.7** **	**118.7** ***

* p<0.05, **p<0.01, *** p<0.001 based on Mann-Whitney U test

Table 2. Baseline-normalized median of β7+ lymphocyte subsets after treatment with MORF-057 BID for 14 days and corresponding RO. § n=4 for 100 mg BID RO.

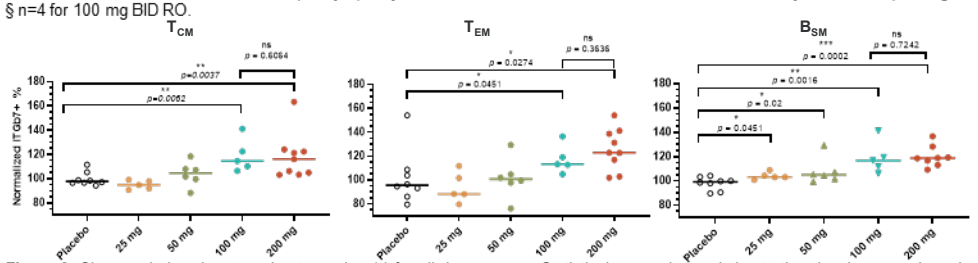

Figure 2. Changes in lymphocyte subsets on day 14 for all dose groups. Statistical comparison relative to the placebo group based on Mann-Whitney U Test.

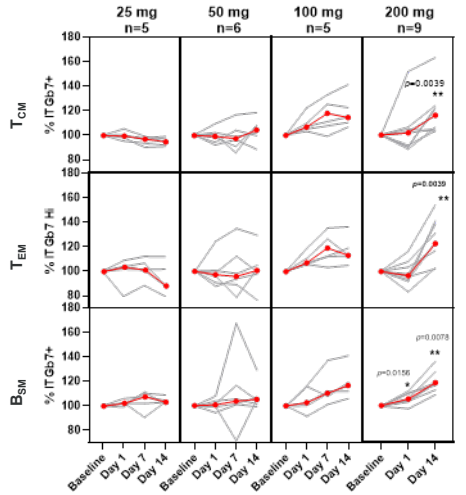

Figure 3. Time-course changes in lymphocyte subset for all dose groups. Statistical comparison relative to baseline based on Wilcoxon Signed Rank Test (Individual data in Gray; Median in Red).

CONCLUSIONS

Healthy subjects receiving MORF-057 for a period of 14 days achieved saturation of α4β7 receptors at the two top dose groups and demonstrated statistically significant increases in circulating ITGβ7 expressing CD4+ T_{CM} and T_{EM} and B_{SM} lymphocyte subsets. No significant differences were observed between the 100 mg and 200 mg dose groups. Effects observed were in line with those reported for biologic inhibitors and small molecules in patients and establish proof of biologic activity for MORF-057, consistent with its proposed mechanism of action.

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Conflict of Interest Statement

All authors were employed by Morphic Therapeutic for the duration of the study
†A.S.R., J.P.J., and A.C. are past employees of Morphic Therapeutic.