

lower MPO activity in both the SmPill®-CyA and Sandimmune® (i.p.) groups relative to untreated mice ( $p<0.05$ ).

Similarly to a reduction in MPO activity, the SmPill®-CyA groups also had reduced IL-1 $\alpha$ , IL-17 and TNF $\alpha$  pro-inflammatory cytokine levels ( $p<0.05$ ) in colon tissue at Day 42.

#### Systemic Tissue Inflammatory Biomarkers:

In a measure of systemic CyA activity, the activity of a number of pro-inflammatory cytokines in activated isolated spleen cells was measured. The Sandimmune® (i.p) treated mice had significantly reduced production of TNF- $\alpha$  ( $p<0.01$ ) and IL-17 ( $p<0.05$ ) relative to cells from the untreated and placebo treated mice. In mice treated with SmPill®-CyA the reduction in TNF- $\alpha$  and IL-17 release by cells was non-significant. The pro-inflammatory cytokine expression levels for Neoral® was between that of Sandimmune® and SmPill®-CyA.

**Conclusion** The above study demonstrated that SmPill®-CyA conferred preferential local colonic efficacy with limited systemic activity, in effect, harnessing the local efficacy of CyA and reducing systemic side effect risks. A SmPill®-CyA formulation, CyCol®, has progressed through human Phase I (PK) study in Canada and Phase IIb study in Ireland and the UK. A multi-centre Phase IIb study is being planned.

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## COLON-TARGETED CYCLOSPORINE IN THE IL10 KNOCK OUT MODEL OF CROHN'S COLITIS

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**Introduction** Cyclosporine A (CyA) is a powerful immunosuppressive agent and has been used off label for steroid-dependent or steroid-refractory ulcerative colitis. However, systemic exposure results in a number of side effects. A novel advanced oral drug delivery system, SmPill®, has been developed to permit targeted release of CyA directly into the colon tissue with limited systemic exposure.

**Aims/Background** The objective was to compare SmPill®-CyA activity in the IL10 knock-out mouse model of Crohn's colitis against the marketed Neoral® (po) and Sandimmun® (ip).

**Method** Mice were treated for 42 days, received the equivalent of 15 mg/kg/day CyA as well as untreated and SmPill® placebo. A secondary objective was to measure systemic pro-inflammatory cytokine activity in isolated spleen cells.

#### Results General Mouse Health:

The SmPill®-CyA group were significantly heavier than mice in all other groups on Day 42.

The SmPill®-CyA group had the lowest Disease Activity Index scores relative to the other groups.

#### Colon Tissue Inflammatory Biomarkers:

The untreated mice had the highest Serum Amyloid A levels (SAA), with the lowest levels seen with those treated with SmPill®-CyA ( $p<0.001$ ) followed by Sandimmun® (i.p) ( $p<0.01$ ) treated mice.

Sandimmun (i.p) and SmPill®-CyA groups had significantly lower ( $P<0.01$ ) histology scores relative to Neoral®. Neoral® (po) had the greatest relative score.

The highest levels of Myeloperoxidase (MPO) activity were seen in the untreated and placebo mice. There was statistically