

# V565, a Novel, Oral Anti-TNF Domain Antibody, Reduces Colonic Mucosal Inflammation in Patients with Ulcerative Colitis.

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## Introduction

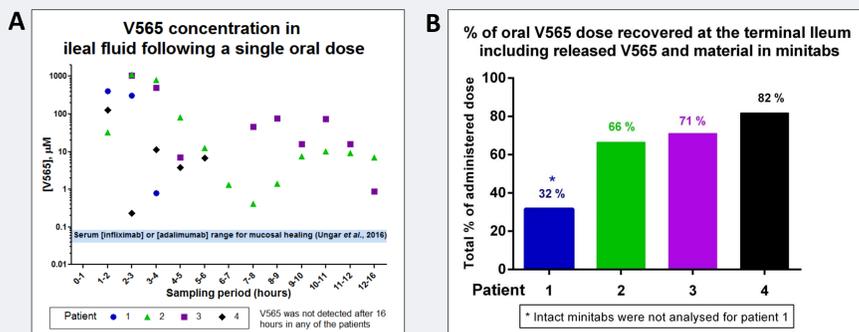
Monoclonal antibodies to TNF have transformed treatment options for patients with Inflammatory Bowel Disease (IBD).

V565 is a novel oral anti-TNF domain antibody (Vorabody) engineered to be resistant to intestinal proteases. It is in development as a potential oral treatment for IBD.

In vitro it suppressed phosphorylation of tyrosine kinases and signalling proteins and inhibited the release of inflammatory cytokines following culture with biopsies taken from patients with UC and CD<sup>1</sup>.

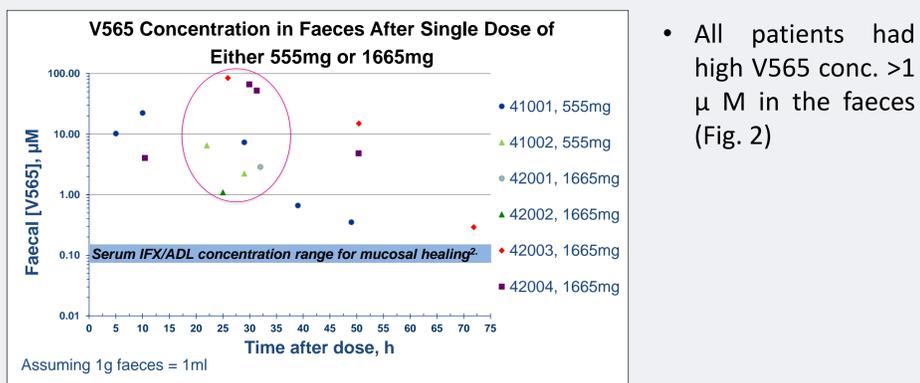
It was safe and well tolerated after high single and multiple doses in healthy volunteers and patient volunteers with CD and resulted in high concentrations of active drug in ileal fluid and faeces (Figure 1, 2).

Figure 1: Four healthy subjects with terminal ileostomies received a single oral dose of 1665mg V565 in encapsulated minitablets. Ileal fluid was collected over 24 hours.



V565 recovered from ileostomies after a single 1665 mg dose, measured by competitive ELISA. A) soluble [V565] in the lumen; B) % of dose recovered, comprising the dissolved V565 in Graph A plus that in partially dissolved mini-tablets.

Figure 2: V565 concentration in faecal samples measured by competitive ELISA. 6 subjects with CD received a single oral V565 dose (2 with 555mg; 4 with 1665mg).



## Aims and Methods

This open label study was designed to demonstrate that orally delivered V565 enters intestinal mucosa and exerts a beneficial effect on inflammatory processes following dosing for 7 days to patients with Ulcerative Colitis.

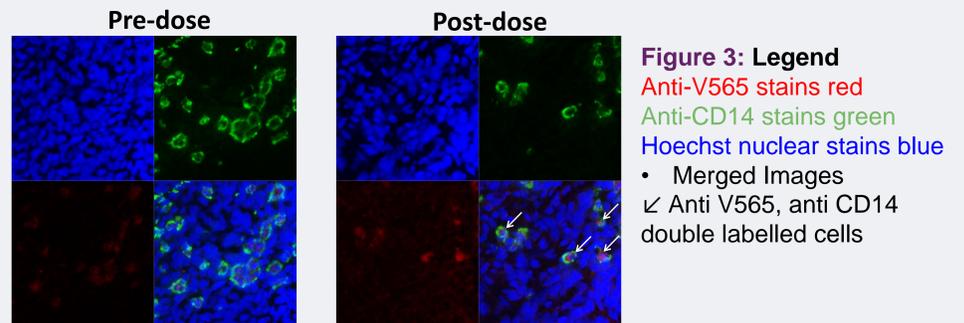
Patients with a Mayo score of 3-10 including an endoscopy score of  $\geq 1$  had up to 7 days of oral dosing with 555mg tid V565. Sigmoidoscopy with biopsies was performed before and after the dosing period.

The primary outcomes of interest were presence of V565 in the mucosa and reduction from baseline in phosphorylation of tyrosine kinases and signalling proteins. Detection of V565 was determined by immunohistochemistry. Phosphorylation was determined using PathScan RTK signalling arrays<sup>2</sup>.

## Results

- 5 patients with UC (Mayo score: 3-7) were treated with oral V565 555 mg three times daily. Due to visit scheduling most received 6 days treatment.
- Presence of V565 was confirmed in the inflamed lamina propria and co-localised with CD14+ macrophages in post-treatment biopsies (Figure 3).

Immunohistochemistry for detection of V565 and CD14+ve cells in colon tissue biopsies after 6 days tid oral dosing of 555 mg V565 demonstrating co-localisation of V565 on CD14+ve macrophages that express transmembrane TNF $\alpha$



- V565 inhibited the phosphorylation of proteins across the array (Fig. 4, 5) in 4 of 5 patients.

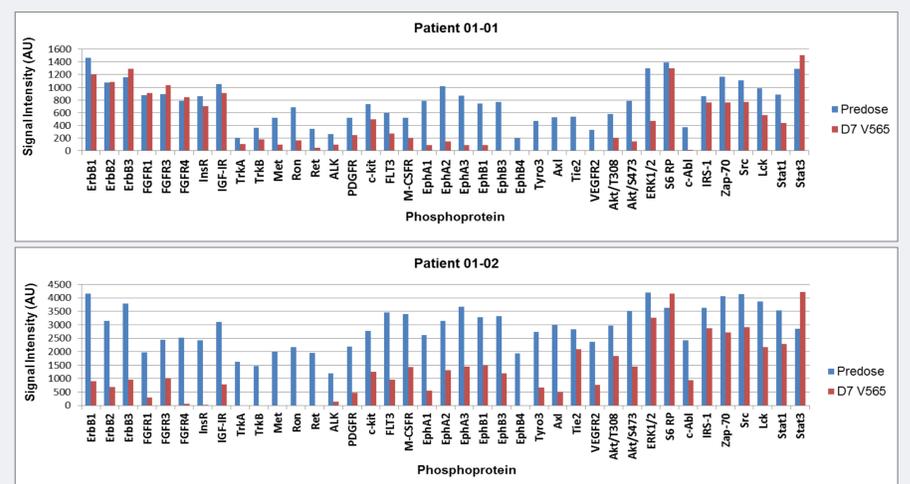


Figure 4: individual phosphoprotein levels in pre- and post-dose inflamed mucosal biopsy samples from 2 patients (representative of the 4). The y-axis shows average pixel intensity for each of the different arrayed phosphoproteins for each sample.

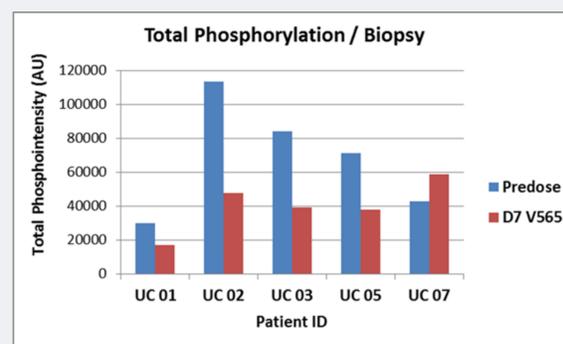


Figure 5: Overall phosphoprotein levels in pre- and post-dose inflamed mucosal biopsy samples demonstrating approximately 50% reduction from baseline after 6-7 days treatment in 4/5 patients

## Conclusions

V565, an oral anti-TNF domain antibody engineered to be resistant to intestinal proteases, was demonstrated bound to CD14+ macrophages in the lamina propria of UC patients and resulted in inhibition of mucosal inflammatory processes after 6-7 days oral dosing.

The reduction of 50% in overall phosphorylation is similar to that seen in an earlier study of UC biopsy cultures with infliximab at a concentration of 67nM (10µg/ml)<sup>1</sup> a serum concentration associated with mucosal healing in IBD patients<sup>3</sup>.

These results provide encouragement that oral dosing with V565 will be a beneficial oral treatment option for patients with IBD.

## References

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- Vossenkamper et al 2014. *Gastroenterology* 147:172-83.
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