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V565 Overview

March 2018

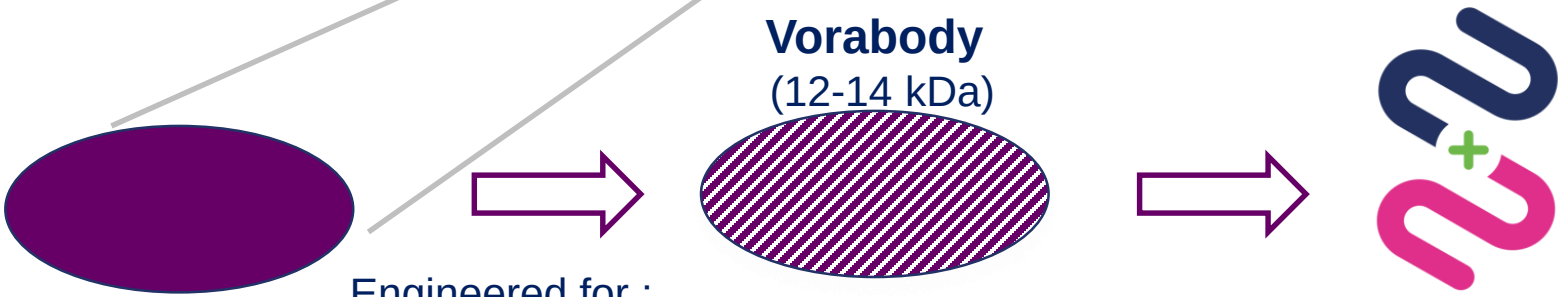
V565: Novel Oral Anti-TNF Domain Antibody Being Studied for the Treatment of IBD

- V565 is the lead compound in the VHsquared portfolio
  - Potent and selective domain antibody to TNF
  - Equipotent to adalimumab in neutralising both membrane and soluble TNF
  - Engineered to be resistant to intestinal and inflammatory proteases and formulated for oral administration
    - High concentrations in the GI tract and minimal systemic exposure
    - Direct access to the inflammation
    - Tolerogenic route of administration

- Expected to deliver the known benefits of anti-TNF monoclonal antibodies in IBD, but without the downsides of parenteral administration and systemic exposure

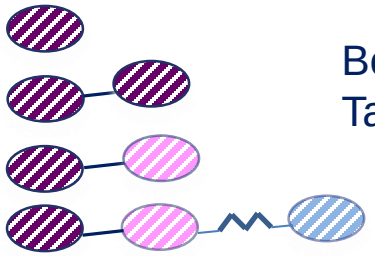
VHsquared's Vorabody Technology Builds on Advantages of Camelid Antibodies

Vorabody
(12-14 kDa)



Engineered for :

- Picomolar affinity
- Intestinal stability
- Efficient yeast production



Bespoke formulation
Targeted delivery

Multiple product formats
Stable or intestinal protease-labile linkers

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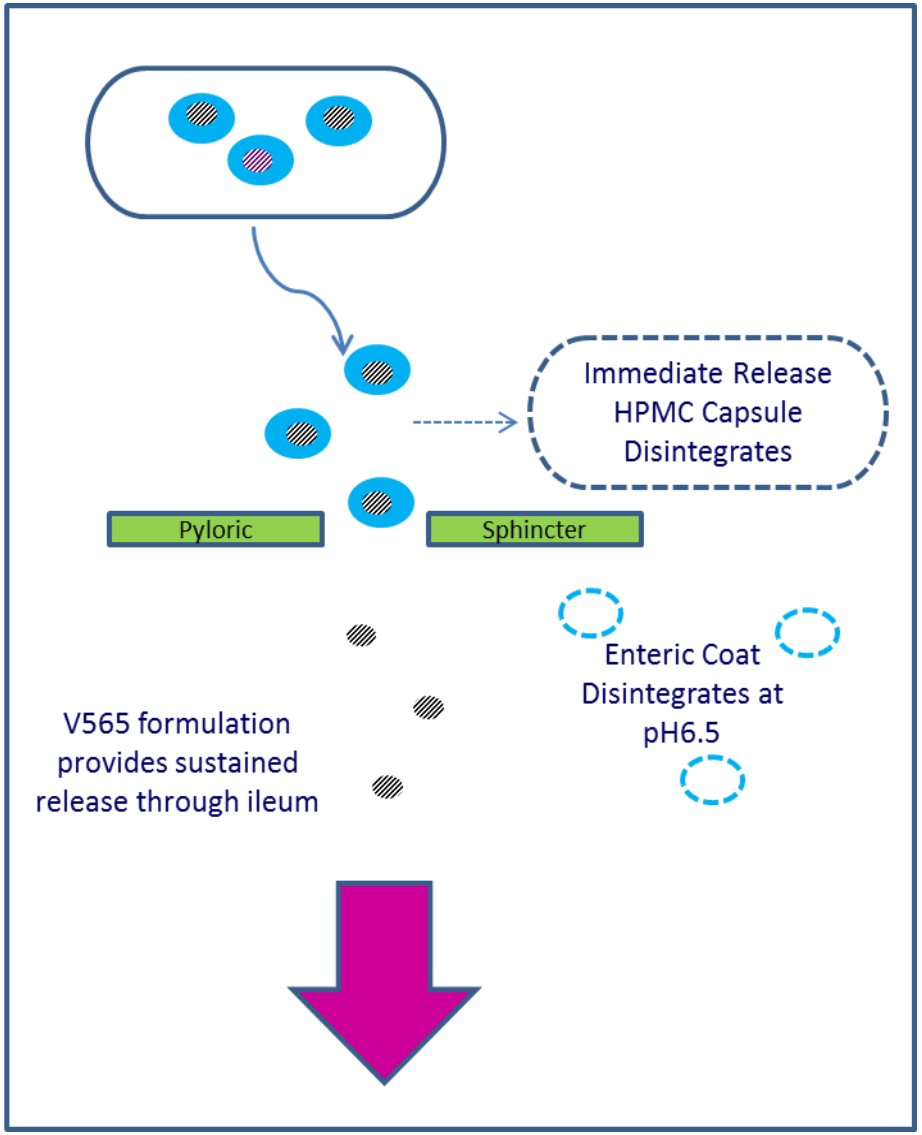
Small Molecule Technology to Deliver a Biological – Proprietary Approach

V565 mini-tablets encapsulated in an immediate release capsule



Targeted delivery:

- Capsule dissolves in stomach releasing enteric coated mini-tablets
- Mini-tablets readily move through the pyloric sphincter
- After they have passed the duodenum, the increase in pH facilitates the disintegration of the enteric coat
- V565 proprietary formulation ensures sustained dissolution of V565 throughout the intestines
- Patent application filed for formulation

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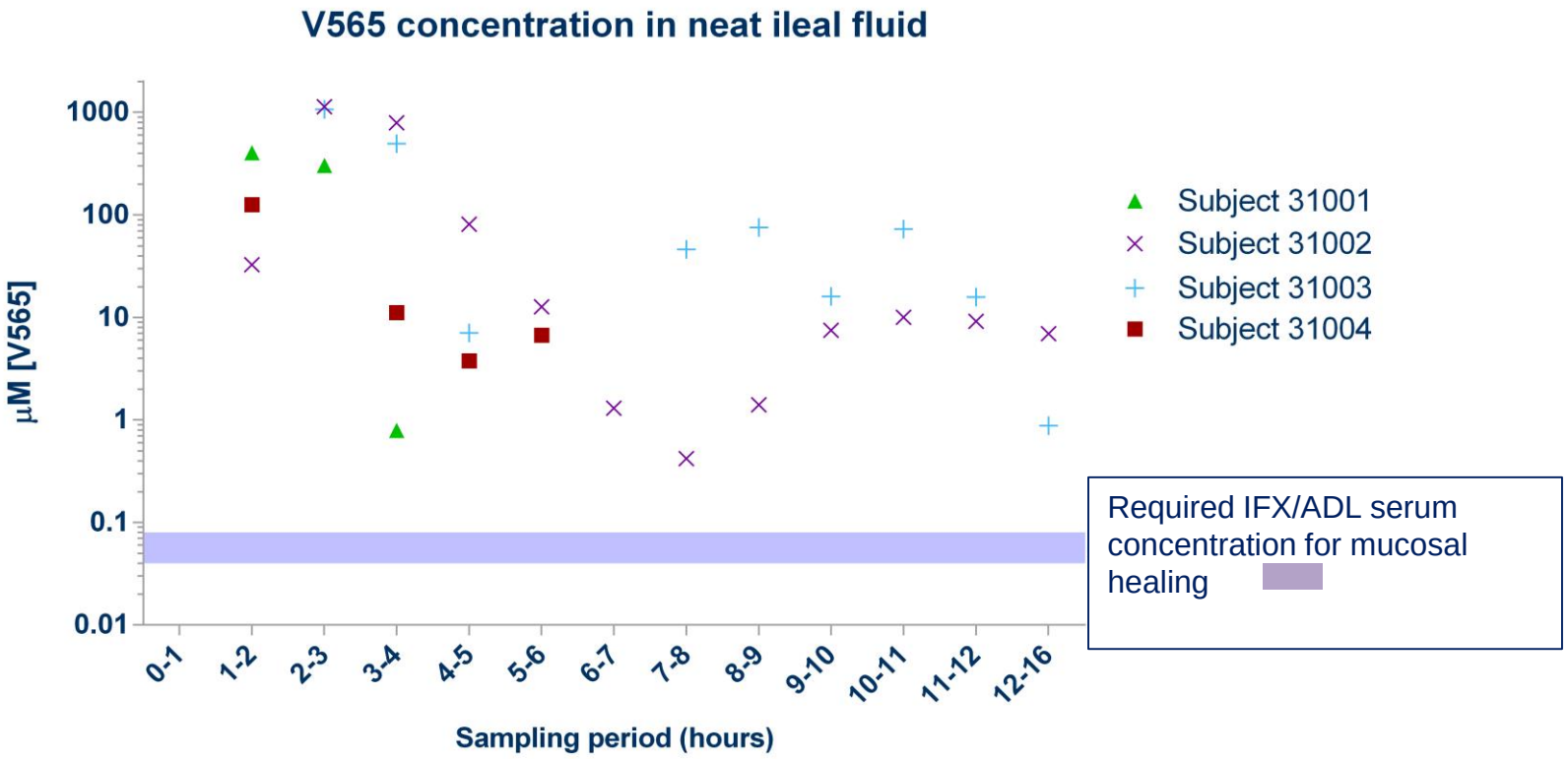
V565: Summary of Key Pre-clinical Features

- Highly potent & specific domain antibody against TNFα, engineered for stability in intestinal tract
- ***Equipotent to Humira – comparable membrane & soluble human TNF neutralisation***
- ***Inhibits spontaneous production of inflammatory biomarkers in ex-vivo Crohn's biopsies***
- Excellent survival in presence of inflammatory proteases (licensed anti-TNF antibodies cleaved)
- Excellent survival in all regions of intestinal tract supernatants - rodent, monkey & human
- Transit to lamina propria of orally administered Vorabody in DSS colitis mice
- ***Very short serum half-life when injected into monkeys (elimination half-life around 50 minutes)***
- ***No treatment-related adverse findings after oral and IV dosing in 6 week toxicity assessment in cynomolgus monkeys or in 6 month toxicity assessment using maximal feasible oral dose***

V565 Clinical Development - V56501 First-in-Human Study

High Concentration of Active V565 Delivered to Terminal Ileum After Oral Dose

- Four subjects (not CD patients) with a terminal ileostomy received a single dose of 1665mg V565
  - Ileal fluid was collected over the next 24 hours to assess V565 concentrations
- High concentrations of active V565 detected in the ileal fluid
- Additional V565 was recovered from undissolved minitabs



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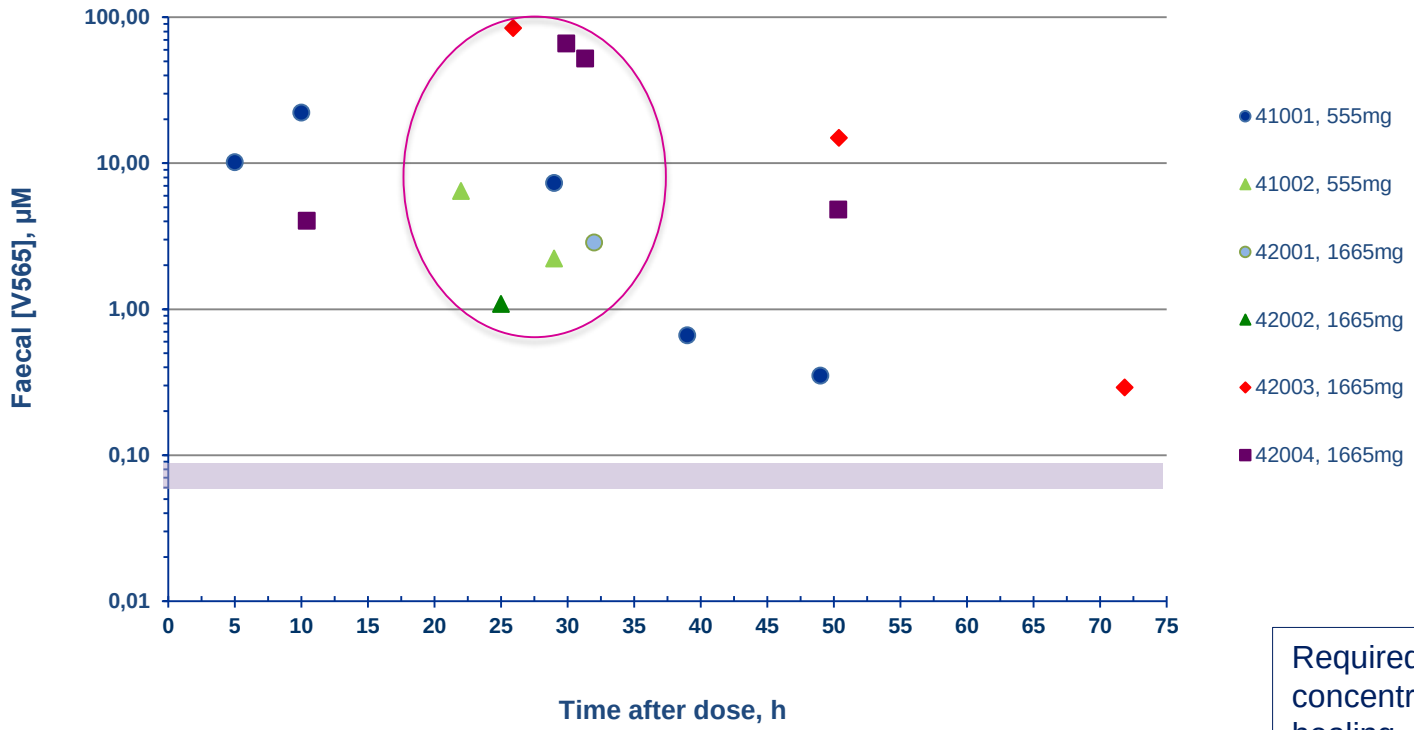
High V565 Faecal Levels c 24h After Single Oral Dose in Crohn‘s Patients

V565 Concentration in Faeces After Single Dose of Either 555mg or 1665mg



Assuming 1g faeces = 1ml

Required IFX/ADL serum concentration for mucosal healing

- High concentrations of active V565 recovered in faeces from all patients around 24h after a single dose

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V565 Clinical Development -
V56503 Human Target Engagement Study

V56503 Designed To Show That Oral V565 Improves Inflammatory Processes

- V56503 is designed to demonstrate that oral dosing to IBD patients improves inflammatory processes in biopsies taken from area of active inflammation

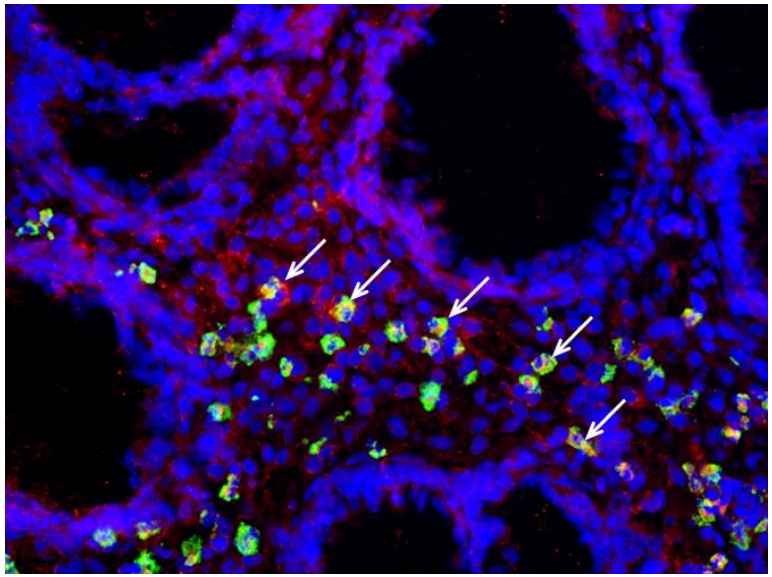
- Primary outcome measures
  - V565 presence in lamina propria and target engagement (binding to mTNF positive cells)
  - Inhibition of phosphorylation array (as used in V565 preclinical studies)

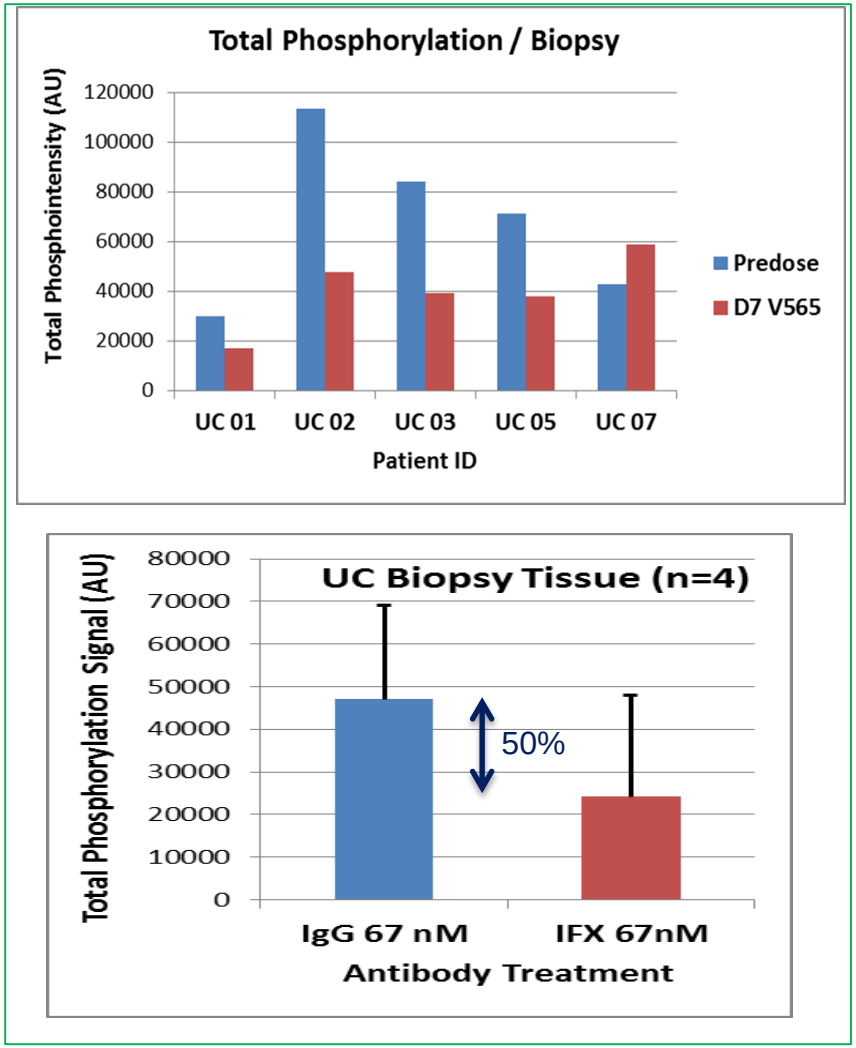
- Open-label exploratory study in five patients with mild to moderate UC

- Main inclusion criteria
  - Established diagnosis of UC for 12 months or more
  - Distal disease, accessible by flexible sigmoidoscopy
  - Mild -moderate UC as defined as Mayo score between 3 – 10, Mayo endoscopic sub score ≥1

- Study Outline
  - Pre-treatment flexible sigmoidoscopy with multiple biopsies at area of active disease
  - Seven days oral dosing with V565 555mg tid (same dose as ongoing CD efficacy trial)
  - Post-treatment flexible sigmoidoscopy with biopsies at same depth as first sigmoidoscopy

V56503 UC Biopsy Study - Target Engagement Demonstrated after Oral Dosing





- Co-location of anti-V565 & anti-CD14 shows V565 has entered site of disease to bind mTNF on macrophages
- Seven days oral dosing with V565 led to 50% reduction in overall phosphorylation in 4/5 patients
  - equivalent to that seen with 67nM infliximab* in earlier biopsy culture study
- Highly encouraging for the demonstration of clinical effectiveness of V565 in IBD
  - Phosphorylation and endoscopic data are consistent in responders and non-responder

* 67nM is serum concentration required for mucosal healing

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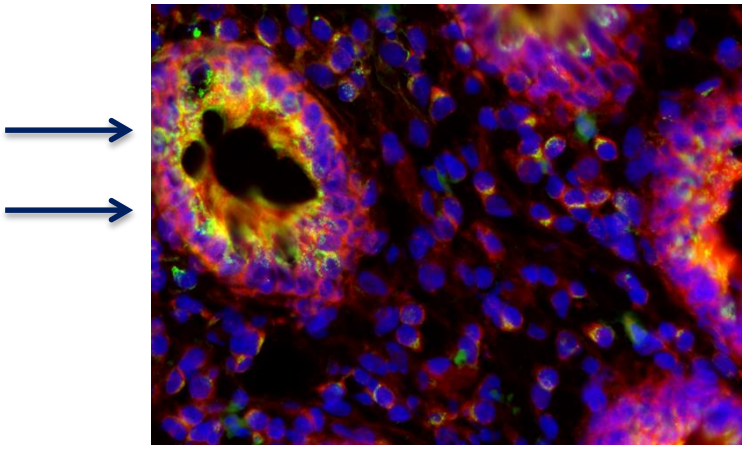
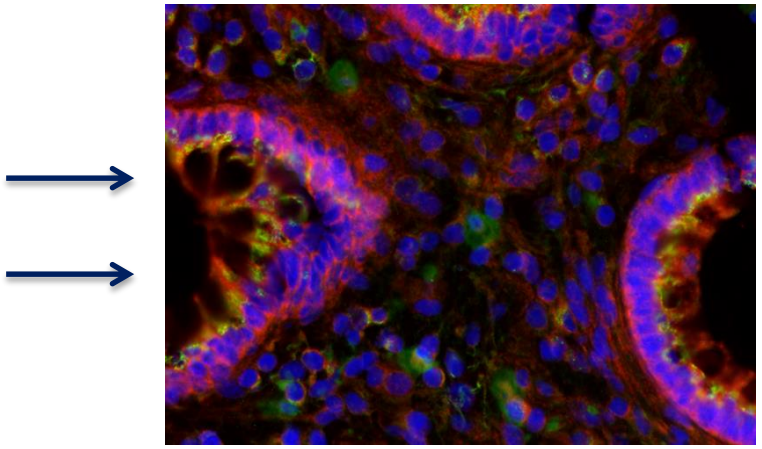
V56503: Other Preliminary Results Support Primary Outcome Measures

Pre-dose



Post-dose



Anti activated Caspase 3 stains yellow/lime green

- Reduction in epithelial Caspase-3 staining indicates reduction in epithelial apoptosis
- Pharmacokinetic results confirm favourable V565 profile as seen in Phase I trial
  - No V565 detected in serum
  - V565 detected in urine of two patients
  - V565 detected in colonic luminal aspirate of 2/3 patients who provided post-treatment samples
    - Patient 7 (non-responder) had no detectable V565 in colonic lumen
- No treatment induced ADAs

V565 Clinical Development -
V56502 Phase II 'HARBOR' Study

V56502 Incorporates Latest Thinking Around IBD Trial Endpoints

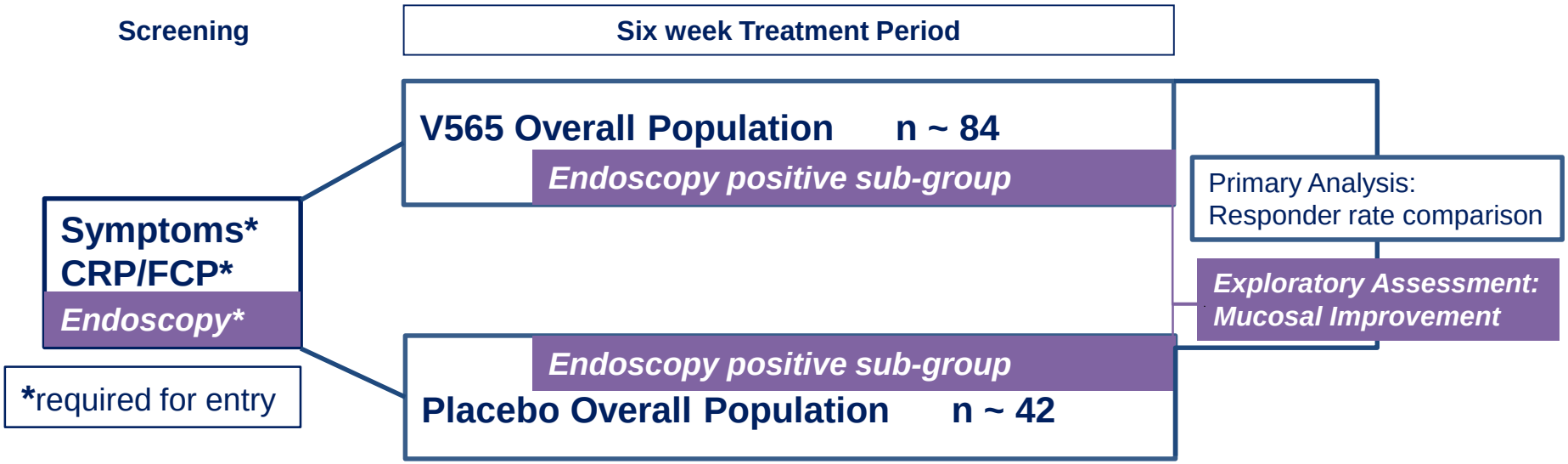
- The IBD product clinical development landscape is changing
  - CDAI is increasingly considered unsuitable as a primary endpoint
  - Regulators expected to require primary endpoint for future Phase III trials to include measure of important symptoms & assessment of inflammation
  - Increasing importance of mucosal healing as measured by endoscopy

- V56502 Phase II study has been designed in line with these considerations

- PoC will be a double blind, placebo controlled, parallel group study in UK, EU and North America
  - Effect of V565 555mg tid vs placebo on symptoms & inflammatory markers
  - Exploratory assessment of mucosal improvement

- Regulatory acceptance in USA, Canada, UK, Germany, Austria, Poland, Czech Republic, Serbia, Slovakia, Hungary, Ukraine, Netherlands, Norway.

V56502 Phase II Outline Design



Responder Definition:
{CDAI <150 or improvement by at least 70points} AND reduction in CRP/FCP

Exploratory blinded pairwise assessment of mucosal appearance in subjects with baseline SES-CD ≥7(ileo/colonic disease) or ≥4(ileal disease only)

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HARBOR Key Selection Criteria

- History of Crohn's disease (confirmed by ileocolonoscopy) of at least **three months'** duration
- CDAI score of ≥220 to ≤450
- CRP ≥5 mg/L (or, if CRP is normal, FCP≥ 250 µg/g)
- Active CD of ileum and/or colon as determined by the baseline ileocolonoscopy
  - Subjects for the exploratory endoscopy sub-study must have a SES-CD ≥7 (or ≥4 if only the ileum is involved)
- Must have failed or experienced intolerance to at least one of the following: aminosalicylates, corticosteroids, immunosuppressants
- Excluded if
  - CD of mouth, oesophagus, stomach or duodenum which is likely to be causing symptoms
  - Isolated recto-sigmoid disease
  - Prior primary efficacy failure or secondary loss of response to anti-TNFα therapy, or any contraindication to anti-TNFα therapy; prior use of any other biologic

V565 Summary

- Potent and selective oral anti-TNF domain antibody
- Safe and well tolerated at high doses
- High concentrations of active drug delivered to GI tract after oral dosing
  - Minimal systemic exposure
- Binds to TNF and reduces inflammation in GI mucosa of UC patients after 6 days oral dosing
- Currently in a multinational Phase II study in Crohn's disease

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