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
**Small Molecule Technology to Deliver a Biological – Proprietary Approach**

**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
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 cynomolagus monkeys or in 6 month toxicity assessment using maximal feasible oral dose**
V565 Clinical Development - V56501 First-in-Human Study
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 were detected in the ileal fluid. Additional V565 was recovered from undissolved minitabs.

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

V565 concentration in neat ileal fluid

- Subject 31001
- Subject 31002
- Subject 31003
- Subject 31004

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
V565 Clinical Development -
V56503 Human Target Engagement Study
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
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.
V56503: Other Preliminary Results Support Primary Outcome Measures

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

Screening

Symptoms* CRP/FCP* Endoscopy*

*required for entry

Six week Treatment Period

V565 Overall Population  n ~ 84

Endoscopy positive sub-group

Placebo Overall Population  n ~ 42

Endoscopy positive sub-group

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

Primary Analysis: Responder rate comparison

Exploratory Assessment: Mucosal Improvement

Exploratory blinded pairwise assessment of mucosal appearance in subjects with baseline SES-CD ≥7(ileo/colonic disease) or ≥4(ileal disease only)
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
V565 Overview
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