Target Engagement and Pharmacodynamic Biomarker Analysis Following Treatment with the Oral Gut-Targeted HIF-1α Stabilizer GB004 in a Phase 1b Trial in Active Ulcerative Colitis

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GB004 Phase 1b Study in Ulcerative Colitis

Background

- UC is associated with a breakdown of the epithelial barrier\(^1\)
- GB004 is an oral small molecule stabilizer of hypoxia inducible factor (HIF-1\(\alpha\)) that targets epithelial repair and function\(^2\)\(^-\)\(^5\)
- GB004 showed preliminary evidence for histologic improvement and clinical activity compared to placebo in a Phase 1b study of UC\(^6\) and as expected, had a gut-targeted PK profile

GB004 Mechanism of Action

Exploratory Biomarkers Measured

- Proportion of HIF-1\(\alpha\) positive and MPO positive cells by IHC
- Levels of fecal calprotectin and fecal secretory IgA
- mRNA expression levels of ITGA6 and TJP1

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Preliminary Evidence for Histologic Improvement and Clinical Activity in Mild-to-Moderate UC Following Treatment with GB004

**Phase 1b Study Design**

**Entry Criteria:**
Mayo Score 3-12 with evidence of active inflammation on baseline colonic biopsy
(RHI > 4 with neutrophils in the epithelium)

**Exploratory Efficacy Endpoints at Day 28**

Note: Mucosal healing, histologic remission, and endoscopic improvement analyzed as achieving endpoint in either sigmoid or rectum; (a) baseline RBS > 0 and/or (b) baseline MES > 0 required to be evaluable for clinical response (a & b), clinical remission (b), and RB endpoints (a).
Modulation of Fecal Secretory IgA and Calprotectin Levels Following Treatment with GB004

Increase in secretory IgA, consistent with improved gut epithelium and local immune defense

Decrease in fecal calprotectin, consistent with reduction in mucosal inflammation

Increase in Median (95% CI) Percent Change from Baseline to Day 28 in Fecal Secretory IgA Levels, GB004 vs Placebo: 87.16% (-215.28%, 389.60%)

Decrease in Median (95% CI) Percent Change from Baseline to Day 28 in Fecal Calprotectin Levels, GB004 vs Placebo: -30.4% (-131.6%, 70.7%)

Difference in medians estimated based on quantile regression employing an optimization algorithm. 95% CIs for difference in median change from baseline based on inverted rank-score method.
Reduction of MPO and Increase of HIF-1α Immunostaining in Biopsies from Sigmoid Colon Following Treatment with GB004

- Reduction of MPO positive cells in sigmoid colon, consistent with **reduction in local mucosal (neutrophilic) inflammation**

- Increase in HIF-1α positive cells in sigmoid colon, consistent with **target engagement**

### Proportion of MPO Positive Cells

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 11)</th>
<th>GB004 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline in MPO Positive Cell Proportions (%)</td>
<td>-7.25% (-20.05, 5.56%)</td>
<td>-2.00% (-8.52, 4.52%)</td>
</tr>
</tbody>
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**Decrease (95% CI) in Mean Change from Baseline to Day 28 in Proportion of MPO Positive Cells in Sigmoid Colon, GB004 vs Placebo:**

### Proportion of HIF-1α Positive Cells

<table>
<thead>
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<th>Placebo (n = 11)</th>
<th>GB004 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline in HIF1α Positive Cell Proportions (%)</td>
<td>+11.43% (-5.04%, 27.91%)</td>
<td>+12.00% (-3.52, 27.52%)</td>
</tr>
</tbody>
</table>

**Increase in Mean Change from Baseline to Day 28 in Proportion of HIF-1α Positive Cells in Sigmoid Colon, GB004 vs Placebo:**

95% CIs for difference in mean change from baseline based on analysis of variance.
Modulation in *ITGA6* and *TJP1* Gene Expression in Biopsies from Sigmoid Colon Following Treatment with GB004

**Increase in TJP1 expression, consistent with **restoring the integrity** of the gut mucosal barrier**

**Increase in ITGA6 expression, consistent with **increased barrier restitution** and migration**

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**Tight Junction Protein-1 (TJP1)**

Increase (95% CI) in Mean log₂-fold change in *TJP1* mRNA expression from Baseline to Day 28 in Sigmoid Colon, GB004 vs Placebo: 0.30 (-0.03, 0.62)

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**Integrin-α6 (ITGA6)**

Increase in Mean (95% CI) log₂-fold change in *ITGA6* mRNA expression from Baseline to Day 28 in Sigmoid Colon, GB004 vs Placebo: 0.26 (-0.06, 0.60)

95% CIs for difference in mean change from baseline based on analysis of variance.
Conclusion

- In this exploratory study GB004, an oral, gut-targeted, HIF-1α stabilizer, demonstrated numeric
  - Increase in HIF-1α positive cells
  - Increases in gene expression (TJP1, ITGA6) and fecal secretory IgA
  - Decreases in MPO positive cells and fecal calprotectin

- These biomarker results, along with trends in clinical activity, suggest that GB004 could improve mucosal healing and reduce inflammation in UC patients

- A Phase 2 study of GB004 in patients with mild-to-moderate UC (SHIFT-UC, NCT04556383, EudraCT 2020-002306-12) is ongoing