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New data suggest Roche's etrolizumab can provide clinically meaningful improvements in the treatment of two of the most common forms of inflammatory bowel disease

- **Roche presents etrolizumab data in Crohn's disease and ulcerative colitis at UEGW**
- **Data suggest etrolizumab leads to endoscopic improvement associated with early symptomatic remission in Crohn's disease and ulcerative colitis**
- **Inflammatory bowel disease affects approximately 3.6 million people across the United States and Europe**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced data from two ongoing phase III trials evaluating etrolizumab in patients with inflammatory bowel disease (IBD). Results from the BERGAMOT and HICKORY trials indicated that patients treated with etrolizumab showed an improvement in both patient reported symptoms and endoscopic assessment of inflammation.^{1,2} Findings were presented at the 25th United European Gastroenterology Week (UEGW) congress, 28 October – 1 November 2017, in Barcelona, Spain.

Data from an exploratory cohort (Cohort 1) of the phase III BERGAMOT study evaluating the safety and efficacy of etrolizumab (105 mg subcutaneous [SC] every 4 weeks [q4w]) or etrolizumab high dose (210 mg SC at weeks 0, 2, 4, 8, and 12) versus placebo in previously treated patients with moderate-to-severe Crohn's disease, suggest an early and persistent symptomatic remission.¹ Key data include:

- Symptomatic remission, defined as unweighted abdominal pain (AP) ≤ 1 and stool frequency (SF) ≤ 3 was achieved with etrolizumab treatment as early as week 6 and was sustained through week 14.¹
- $\geq 50\%$ improvement in endoscopically assessed inflammation and ulceration was measured using the Simple Endoscopic Score for Crohn's Disease (SES-CD) in 21.0% and 17.4% of patients receiving etrolizumab 105 mg and 210 mg respectively, compared with 3.4% receiving placebo at week 14.¹

This study utilised assessment of endoscopic videos by an independent panel of expert central readers blinded to patient's treatment assignment.¹ Approximately 75% of the patients in this cohort had previous

failure of aTNF therapy.¹ These results will help refine and finalise the endpoints used for the pivotal cohort (Cohort 3) of the BERGAMOT trial.

In patients with moderate-to-severe UC and prior aTNF failure, updated results from the open label induction cohort (130 patients treated with etrolizumab 105 mg q4w for 14 weeks) within the phase III HICKORY study were also presented, suggesting that treatment with etrolizumab resulted in a clinically meaningful improvement as observed in endoscopic improvement as well as clinical response and remission.²

- At week 14, etrolizumab was associated with a clinical response in 50.8% of patients.²
- A total of 43.9% of patients had a ≥ 1 -point improvement from baseline in the endoscopic score, which was associated with increased remission rates with regard to rectal bleeding and stool frequency.²

Both studies found that etrolizumab was well tolerated, with a frequency of adverse events comparable with placebo.^{1,2}

“Management of inflammatory bowel disease is challenging, as only around half of patients will achieve a response or remission with current therapies,” said Sandra Horning, M.D., Roche’s Chief Medical Officer and Head of Global Product Development. “We are encouraged by these early data across both ulcerative colitis and Crohn’s disease, which highlight the potential of etrolizumab as a much needed new treatment option for these patients.”

BERGAMOT and HICKORY are part of a global phase III clinical development programme for etrolizumab in patients with UC and Crohn's disease, which aims to assess important clinical questions in IBD.^{3,4} It is the first clinical development programme to address a number of key questions in phase III studies:

- First to evaluate endoscopic improvement in Crohn’s disease
- First head-to-head comparison vs both adalimumab and infliximab in randomised, controlled studies in UC
- First to assess the potential for predictive biomarkers in UC and Crohn’s disease
- First monthly subcutaneously administered anti-integrin therapy

The etrolizumab programme will enrol more than 3,400 patients across eight pivotal phase III studies, for UC and Crohn's disease.

About BERGAMOT⁵

BERGAMOT is a phase III multi-centre, double-blind, randomised, placebo-controlled study evaluating the efficacy and safety of etrolizumab during induction and maintenance in patients with moderate-to-severe Crohn's disease who have been previously treated with immunosuppressants, corticosteroids, and/or anti-tumour necrosis factor (aTNF) inhibitors. The study was designed with three sequential induction cohorts and a single maintenance cohort;

- **Cohort 1:** A proof of concept induction cohort (n=300) where patients will be treated with placebo, etrolizumab (105 mg SC q4w) or etrolizumab high dose (210 mg SC at weeks 0, 2, 4, 8, and 12) for a 14-week induction phase
- **Cohort 2:** An open-label induction cohort (n=350) where patients are randomised between etrolizumab (105 mg SC q4w) or etrolizumab high dose (210 mg SC at weeks 0, 2, 4, 8, and 12)
- **Cohort 3:** The pivotal induction cohort (n=600), where patients will receive placebo, etrolizumab (105 mg SC q4w) or etrolizumab high dose (210 mg SC at weeks 0, 2, 4, 8, and 12) for 14 weeks.

Patients in the etrolizumab arms of any of the induction cohorts who are responders at week 14 are re-randomised 1:1 to placebo or etrolizumab (105 mg SC q4w) for a maintenance phase of ≥ 52 weeks.

About HICKORY⁶

HICKORY is an ongoing phase III, multi-centre, double-blind, placebo-controlled study evaluating the safety, efficacy, and tolerability of etrolizumab during induction (week 14) and maintenance of remission (week 66) compared with placebo in patients with moderate-to-severe UC who have had a previous failure of aTNF therapy. Results from the open label induction cohort (n=130) were presented at UEGW. In the pivotal induction cohort, patients (n=670) will be randomised in a 4:1 ratio to receive either etrolizumab (105mg SC q4w) or placebo in a 14-week double-blind induction phase.

Patients who are clinical responders at week 14 from both cohorts will be randomised in a 1:1 ratio to receive either etrolizumab or placebo for a 52-week double-blind maintenance phase (from weeks 14 to 66).

About etrolizumab

Etrolizumab is an investigational dual action anti-integrin antibody designed to selectively control disease in the gut of patients with moderate-to-severe inflammatory bowel disease (UC or Crohn's disease).⁷

Etrolizumab is thought to work by selectively targeting and attaching to a specific part ($\beta 7$ subunit) of two key proteins ($\alpha 4\beta 7$ and $\alpha E\beta 7$ integrins) found on cells that play a key role in inflammation in IBD.^{7,8} With this dual mechanism of action etrolizumab has been designed with the objective of preventing inflammatory cells from entering and being retained in the gut.^{7,8} Etrolizumab can be self-administered once per month via the subcutaneous route, which means the drug is injected under the skin (tissue layer between the skin and muscle).^{9,10}

Roche and Genentech have launched an extensive phase III clinical development programme, assessing the efficacy and safety of etrolizumab in patients with UC and Crohn's disease,^{3,4} which aims to address significant clinical unmet needs in the treatment of these diseases.

Ulcerative colitis:

- Five randomised controlled trials (HIBISCUS I, HIBISCUS II, GARDENIA, LAUREL and HICKORY) and a rollover open label extension study (COTTONWOOD).
- The HIBISCUS I & II, GARDENIA and LAUREL studies are assessing patients with moderately-to-severely active UC who are naïve to aTNFs.
- The HICKORY study is assessing patients with moderately-to-severely active UC with prior aTNF failure.

Crohn's:

- A randomised controlled trial (BERGAMOT) and a rollover open label extension study (JUNIPER) will investigate etrolizumab in patients with moderately-to-severely active Crohn's disease.

About inflammatory bowel disease

IBD describes a group of diseases that involve chronic inflammation of the digestive tract with UC and Crohn's being the two main types.¹¹ UC is largely limited to the colon or large intestine and is characterised by a continuous pattern of ulcerations to the mucosal layer of the gut.¹² Crohn's disease can affect any part of the digestive tract from the mouth to the anus and it is characterised by inflammation that spans the intestinal wall and by skip lesions, which are intermittent areas of inflammation with healthy tissue present in between.¹² In a healthy person the immune system usually attacks and kills foreign invaders, such as bacteria,

viruses, and other microorganisms.^{12,13} However, in people with IBD, the immune system mounts an inappropriate response in the intestinal tract, resulting in prolonged inflammation.^{12,13}

IBD is most common in developed countries, with approximately 3.6 million people in the United States and Europe living with the disease (1.4 million and 2.2 million, respectively)¹⁴ and the disease has an increased rate of diagnosis in adults between 15 and 35 years old.¹² Despite patients with IBD being expected to have a normal life expectancy, a patient's quality of life can be significantly compromised.¹⁵

About Roche in GastroImmunology™

Leveraging an established heritage of immunology, innovation, and personalised healthcare, Roche GastroImmunology™ is dedicated to following the science to improve patients' lives.

Roche GastroImmunology™ is committed to

- Clinical and preclinical research of molecules with unique mechanisms of action
- Exploring novel biomarkers to personalise care for patients
- Validating and refining endpoints to assess the most clinically relevant outcomes
- Understanding the underlying causes of IBD to change the course of the disease

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Roche has been recognised as the Group Leader in sustainability within

the Pharmaceuticals, Biotechnology & Life Sciences Industry nine years in a row by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2016 employed more than 94,000 people worldwide. In 2016, Roche invested CHF 9.9 billion in R&D and posted sales of CHF 50.6 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

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