Evaluate Vantage

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Roche’s test of novel gut target nears

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Pivotal ulcerative colitis data on etrolizumab, a dual-action anti-integrin antibody, are due soon, and Roche has Takeda’s Entyvio in its sights.

The first phase III data from Roche’s ulcerative colitis programme with etrolizumab could come by mid-year. Five studies are being run and, while etrolizumab should comfortably be able to demonstrate its utility in placebo-controlled trials, it will face a tougher task when it comes up against active controls, in this case Remicade or Humira.

Targeting integrins is not a new mechanism for gastrointestinal agents: Takeda’s Entyvio, an alpha-4 beta-7 integrin antibody, is on the market for ulcerative colitis and Crohn’s disease. However, etrolizumab is novel because it targets a second integrin, and the pivotal programme needs to show that this bestows important differentiation.

Project	Etrolizumab
Company	Roche
NPV	$3.0bn
% of market cap	1%
Event	Data from five phase III trials
Date	Mid-2020

Initial results from one of Roche’s phase III studies, Hickory, emerged in 2017. That tested etrolizumab versus placebo in patients with mild to moderate ulcerative colitis who had failed to respond to anti-TNF therapy.

In the open-label induction cohort of 130 subjects etrolizumab was associated with a 14-week clinical response in 50.8% of patients; 43.9% of patients had an improvement of at least one point from baseline in the endoscopic score. Etrolizumab was well tolerated, with a frequency of adverse events comparable to placebo.

Takeda’s Entyvio was approved in ulcerative colitis based on two integrated placebo-controlled studies in a total of 895 patients. Response rates at week six were 47.1%, versus 25.5% for placebo ($p<0.001$). At week 52, 41.8% of patients who continued to receive Entyvio every eight weeks were in clinical remission, versus 15.9% of those who switched to placebo ($p<0.001$).

In reality, however, etrolizumab is not just up against placebo, and it is notable that Roche has pitted it against older anti-TNF agents rather than the newer mechanisms that are seen dominating this market in the coming years. Either way, some analysts believe that the antibody has a good chance of beating Humira in the Hibiscus studies, though showing superiority to Remicade in Gardenia be tougher.

In Remicade's own ulcerative colitis trials, in a total of 728 patients, 62-69% treated with the drug had a clinical response at week eight, versus 29-37% of those on placebo ($p<0.001$). At week 54, 34-35% of patients who continued to receive Remicade every eight weeks were in clinical remission, as compared with 17% on placebo ($p<0.01$).

Newer mechanisms are set to dominate the ulcerative colitis market by 2026

Product	Company	Mechanism of action	2020e ($m)	2026e ($m)	Indication status
Rinvoq	Abbvie	Jak1 inhibitor	-	1,721	Phase III
Stelara	Johnson & Johnson	IL-12 and IL-23 antibody	296	1,158	Marketed
Entyvio	Takeda	Alpha-4 beta-7 integrin antibody	1,821	1,118	Marketed
Etrolizumab	Roche	Alpha-4 beta-7 integrin antibody; alpha-E beta-7 integrin antibody	-	891	Phase III
Zeposia	Bristol-Myers Squibb	S1P receptor 1 regulator; S1P receptor 5 regulator	-	859	Phase III

Source: EvaluatePharma.

As a dual-action anti-integrin antibody etrolizumab targets the alpha-4 beta-7 and alpha-E beta-7 integrins, and is said to work by preventing inflammatory cells from entering and being retained in the gut.

Entyvio is forecast to be the market leader in this mechanism in 2026, with ulcerative colitis sales of $1.1bn, according to *EvaluatePharma* data. Despite the absence of confirmatory phase III data, the sellside has etrolizumab not far behind, with sales at $891m pencilled in for the same year.

On etrolizumab's side is convenience, since it is administered as a once-monthly subcutaneous injection while Entyvio is administered intravenously. Takeda has developed a subcutaneous version of Entyvio, but that received a CRL in December; the drug has had better luck in Europe, with an approval last week.

Roche hopes to file etrolizumab in ulcerative colitis this year. The company needs to make more than a convenience argument to succeed in a highly competitive market against very effective newer agents, however, and the approaching readouts will help determine what the project is capable of.

Phase III studies of etrolizumab			
Trial	**Details**	**Number of patients**	**Primary completion**
Ulcerative colitis			
Hibiscus I	TNF-naïve, induction, vs. Humira	358	Feb 2020
Hibiscus II	TNF-naïve, induction, vs. Humira	358	Mar 2020
Gardenia	TNF-naïve, sustained remission, vs. Remicade	390	Apr 2020
Laurel	TNF-naïve, maintenance, vs. placebo	359	Apr 2020
Hickory	Prior TNF failure, induction and maintenance, vs. placebo	609	Apr 2020
Cottonwood	Rollover open-label extension study	2,100	Aug 2025
Crohn's disease			
Bergamot	Induction and maintenance treatment	1,150	Jun 2021
Juniper	Rollover open-label extension study	900	Oct 2025
Sources: clinicaltrials.gov & Jefferies.			