NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
December 2022

Filgotinib for treating moderately to severely active Crohn's disease

Company/Developer	Galapagos NV

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 9613	NICE ID: 10168	UKPS ID: 652705

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Filgotinib is being developed for adults with moderately to severely active Crohn's disease. Crohn's disease is a type of inflammatory bowel disease which can affect any part of the digestive system. Crohn's disease causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. Symptoms include abdominal pain, diarrhoea, weight loss and fatigue. There is no cure for Crohn's disease so treatment options focus on managing and relieving symptoms. Patients may have periods of time when they are not suffering from symptoms (remission) or have flare-ups of symptoms (relapses). Additional treatments are required for Crohn's disease, as some patients do not respond well to some of the current therapy options.

Filgotinib, the active substance in Jyseleca, reduces the activity of the immune system. It does this by blocking the action of enzymes known as Janus kinases (JAKs). These enzymes play an important role in the inflammatory processes that occur in rheumatoid arthritis and ulcerative colitis. By blocking the enzymes' action, filgotinib can help to reduce symptoms of these diseases. If licensed, filgotinib will offer an additional orally administered treatment option for the induction and maintenance of remission in adults with moderately to severely active Crohn's disease.

Proposed Indication

Treatment of moderately to severely active Crohn's disease.[1]

Technology

Description

Filgotinib (GLPG-0634, Jyseleca), is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of the JAK family. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane. JAK1 is important in mediating inflammatory cytokine signals, JAK2 in mediating myelopoiesis and erythropoiesis and JAK3 plays critical roles in immune homeostasis and lymphopoiesis. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Filgotinib modulates these signalling pathways by preventing the phosphorylation and activation of STATs. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed > 5-fold higher potency of filgotinib for JAK1 over JAK2, JAK3 and TYK2. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3-mediated signalling downstream of the heterodimeric cytokine receptors for interleukin (IL)-2, IL-4 and IL-15, JAK1/2-mediated IL-6, and JAK1/TYK2-mediated type I interferons, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2. GS-829845, the primary metabolite of filgotinib, was approximately 10-fold less active than filgotinib in in vitro assays, while exhibiting a similar JAK1 preferential inhibitory activity. In an in vivo rat model, the overall pharmacodynamics effect was predominantly driven by the metabolite.[2]

Filgotinib is currently in clinical development for the treatment of moderately to severely active Crohn's disease in participants who are biologically-naïve and biologically-experienced.[1] In the phase III trial (DIVERSITY1, NCT02914561), filgotinib is administered orally once daily at either 100mg or 200mg for 10 weeks.[1]

Key Innovation

Despite the current array of treatment options for Crohn's disease, remission rates in induction trials are still less than 50%, revealing a therapeutic ceiling in the management of the disease.[3] In recent years, drug development has shifted from monoclonal antibodies to small molecules agents. Unlike antibodies, small molecules are able to cross the sphingolipid cell membrane and exert their effect inside the cell. Their molecular characteristics and size allow a more convenient oral administration and avoid the development of antidrug antibodies. Among the most promising families of small molecules is that of JAK inhibitors.[4] Unlike some of the other medications taken by mouth such as thiopurines (6-mercaptourine and azathioprine) and methotrexate that take several weeks to control inflammation, JAK inhibitors work more quickly to achieve and maintain remission.[5] If licensed filgotinib will offer an additional treatment option for patients with moderately or severely active Crohn's disease.

Regulatory & Development Status

Filgotinib currently has Marketing Authorisation in the EU/UK for the following indications:[2]

- Treatment of moderately to severely active rheumatoid arthritis
- Treatment of moderately to severely active ulcerative colitis

Filgotinib is in phase II/III clinical development for:[6]

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis

- Sjogren's syndrome

Patient Group

Disease Area and Clinical Need

Crohn's disease (CD) can affect any part of the digestive system,[7] and causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. Main symptoms of CD are abdominal pain, diarrhea, weight loss and fatigue.[8,9] CD is more common in urban areas, and in northern, developed countries such as Northern Europe, particularly amongst white people of European descent. The exact cause of CD is unknown but there are several factors that could contribute to its development, including: inheritance, immune response issues, smoking, gut viruses, abnormal balance of gut bacteria, and stress.[8,10]

Crohn's disease affects around 1 in 650 people in the UK.[11] In England, in 2021-22, there were 151,340 finished consultant episodes (FCE) and 140,775 admissions for Crohn's disease (ICD-10: K50) which resulted in 85,964 FCE bed days and 126,981 day cases.[12] CD has increased over the past two decades at a rate of 2-3% per annum and is predicted to reach a prevalence of 487.2 per 100,000 by 2025. CD is also associated with an increased risk of all-cause mortality.[13]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for the treatment of moderately or severely active Crohn's disease:[14]

- Anti-inflammatories, such as sulfasalazine, mesalamine and olsalazine
- Steroids, such as prednisolone
- Immunosuppressants, such as azathioprine, mercaptopurine and methotrexate
- Biological medicines, such as adalimumab, infliximab, vedolizumab and ustekinumab
- Antibiotics, such as metronidazole and ciprofloxacin

Clinical Trial Information

Trial	**DIVERSITYLTE, NCT02914600, EudraCT 2016-002763-34**; A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects With Crohn's Disease. **Phase III:** Enrolling by invitation **Locations:** 22 European countries, UK, Australia, USA and other countries **Primary completion date:** May 2025
Trial Design	Non-randomised, parallel assignment, double masked
Population	N=1,000 (estimated); must have enrolled in a Gilead-sponsored Crohn's disease parent protocol (NCT03046056 and NCT03077412), females of childbearing potential must have a negative pregnancy test at day 1.
Intervention(s)	Filgotinib (orally administered once daily, 200mg or 100mg)
Comparator(s)	Matched placebo (orally administered once daily, 200mg or 100mg)
Outcome(s)	Primary outcome measures:

	Induction study: • Proportion of participants achieving clinical remission by Crohn's disease activity index (CDAI) at week 10 [Time frame: week 10] • Proportion of participants achieving endoscopic response at week 10 [Time frame: week 10] Maintenance Study: • Proportion of participants achieving clinical remission by CDAI at week 58 [Time frame: week 58] • Proportion of participants achieving endoscopic response at week 58 [Time frame: week 58] • See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**DIVERSITY1**, NCT02914561, EudraCT 2016-001367-36; Combined Phase 3, Double-blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects With Moderately to Severely Active Crohn's Disease **Phase III:** Completed **Location(s):** 24 EU countries, UK, Australia, USA and other countries **Study completion date:** November 2022
Trial Design	Randomised, parallel assignment, double masked
Population	N=1374 (actual); Males or non-pregnant, non-lactating females, ages 18-75 years, documented Crohn's disease with a minimum disease duration of 3 months, moderately to severely active Crohn's disease.
Intervention(s)	Filgotinib (orally administered once daily, 200mg or 100mg)
Comparator(s)	Matched placebo (orally administered once daily)
Outcome(s)	Primary outcome measures: Induction study: • Proportion of participants achieving clinical remission by Crohn's disease activity index (CDAI) at week 10 [Time frame: week 10] • Proportion of participants achieving endoscopic response at week 10 [Time frame: week 10] Maintenance Study: • Proportion of participants achieving clinical remission by CDAI at week 58 [Time frame: week 58] • Proportion of participants achieving endoscopic response at week 58 [Time frame: week 58] • See trial record for full list of outcomes.

Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**DIVERGENCE2**, NCT03077412, EudraCT 2016-003153-15; A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Filgotinib in the Treatment of Perianal Fistulizing Crohn's Disease. **Phase II:** Completed **Locations:** 6 European countries, UK, Canada and the USA **Study completion date:** January 2021
Trial Design	Randomised, parallel assignment, double masked
Population	N=57 (actual); males or non-pregnant, non-lactating females, ages 18 to 75 years, diagnosis of Crohn's disease with a minimum duration of Crohn's disease of at least 3 months.
Intervention(s)	Filgotinib (orally administered once daily, 200mg or 100mg)
Comparator(s)	Matched placebo (orally administered once daily)
Outcome(s)	Primary outcome measure: • Percentage of participants who achieved combined fistula response at week 24 [Time frame: week 24] See full trial record for full list of outcomes.
Results (efficacy)	Overall, 91.2% of patients had complex perianal fistulae and TNFi treatment had previously failed in 64.9% of patients. A lower proportion of patients randomised to receive filgotinib 200 mg discontinued the study compared with those who received placebo. The proportion of patients who achieved a combined fistula response at week 24 was numerically higher in the filgotinib 200 mg group (47.1%; 90% confidence interval [CI]: 26.0–68.9) than in the placebo group (25.0%; 90% CI: 7.2–52.7), with similar results observed for combined fistula remission.[15]
Results (safety)	Treatment-emergent severe adverse events were highest in the filgotinib 200 mg group. Adverse event rates were otherwise similar across treatment groups.[15]

Clinical Trial Information	
Trial	**DIVERGENCE 1**, NCT03046056, EudraCT2016-003179-23; A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Filgotinib in the Treatment of Small Bowel Crohn's Disease (SBCD). **Phase II:** Completed **Locations:** 7 EU countries, UK, Canada and USA **Study completion date:** July 2020
Trial Design	Randomised, parallel assignment, double masked

Population	N=78 (actual); Males or non-pregnant, non-lactating females, ages 18 to 75 years, moderately or severely active Crohn's disease, minimum duration of Crohn's disease of at least 6 months.
Intervention(s)	Filgotinib (orally administered once daily, 200mg or 100mg)
Comparator(s)	Matches placebo (orally administered once daily)
Outcome(s)	Primary outcome measures: • Percentage of participants who achieved clinical remission at week 24 [Time frame: week 24] See full trial record for full list of outcomes.
Results (efficacy)	A total of 122 (median disease duration: 7 months) patients were included, corresponding with 379 diseased segments. The median (IQR) CDEIS scores at week 0, 12, and 54 were 9.9 (6.1–14.4), 2.4 (0.2–4.6), and 0.2 (0.0–3.7), respectively. At weeks 12 and 54, the rates of endoscopic healing and complete endoscopic remission were 41% and 61% and 61% and 73%, respectively. Median CDEIS scores were similar among patients with deep ulcers at baseline and those with only superficial ulcers at week 12 and 54. Segmental remission rates were lower both at week 12 and 54 in the ileum compared with colonic segments ($P < 0.01$ all comparisons) and in the rectum ($P = 0.02$ and $P = 0.03$).[16]
Results (safety)	In biologic-naive patients with CD treated with IFX combo therapy, the severity of endoscopic lesions at the baseline did not influence healing rates. Endoscopic remission occurs less frequently in the ileum compared with the colon.[16]

Clinical Trial Information	
Trial	NCT02048618, EudraCT2013-002857-32; Double-Blind, Randomized, Placebo-Controlled, Multi-Centre Study to Investigate the Efficacy and Safety of GLPG0634 in Subjects With Active Crohn's Disease With Evidence of Mucosal Ulceration. **Phase II:** Completed **Locations:** 9 EU countries and UK **Study completion date:** November 2015
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N=175 (actual); male or female subjects between 18 and 75 years, documented history of ileal, colonic or ileocolonic Crohn's disease, evidence of active inflammation, subjects previously not exposed to anti-TNF treatment.
Intervention(s)	Filgotinib (orally administered once daily, 200mg or 100mg)
Comparator(s)	Matched placebo (orally administered once daily)
Outcome(s)	Primary outcome measure: • Percentage of subjects achieving clinical remission at week 10 [Time frame: week 10]

	See full trial record for full list of outcomes.
Results (efficacy)	In the intention-to-treat population, 60 (47%) of 128 patients treated with filgotinib 200 mg achieved clinical remission at week 10 versus 10 (23%) of 44 patients treated with placebo (difference 24 percentage points [95% CI 9-39], p=0·0077).[17]
Results (safety)	In a pooled analysis of all periods of filgotinib and placebo exposure over 20 weeks, serious treatment-emergent adverse effects were reported in 14 (9%) of 152 patients treated with filgotinib and three (4%) of 67 patients treated with placebo.[17]

Estimated Cost

Filgotinib is already marketed in the UK for the treatment of rheumatoid arthritis and ulcerative colitis, a pack of 30 x 100 or 200mg tablets costs £863.10.[18]

Relevant Guidance

NICE Guidance

- Nice Technology appraisal guidance in development: Etrolizumab for previously treated moderately to severely active Crohn's disease (TA10997). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development: Upadacitinib for previously treated moderately to severe active Crohn's disease (TA10997). Expected June 2023.
- NICE Technology appraisal guidance: Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986] (TA10884). Expected March 2023.
- NICE Technology appraisal guidance: Darvadstrocel for treating complex perianal fistulas in Crohn's disease (TA556). January 2019.
- NICE Technology appraisal guidance: Ustekinumab for moderately to severely active Crohn's disease after previous treatment (TA456). July 2017.
- NICE Technology appraisal guidance: Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (TA352). August 2015.
- NICE Technology appraisal guidance: Infliximab and adalimumab for the treatment of Crohn's disease (TA187). May 2010.
- NICE Technology appraisal guidance: The clinical effectiveness and cost effectiveness of infliximab for Crohn's disease (TA40). April 2002.
- NICE Clinical Guideline: Crohn's disease: Management (CG152). October 2012.
- NICE Diagnostic guidance: PredictSURE IBD and IBDX to guide treatment of Crohn's Disease (DG45). February 2022.
- NICE Interventional procedures guidance: Extracorporeal photopheresis for Crohn's Disease (IPG288). February 2009.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Colorectal: Complex Inflammatory Bowel Disease (Adult). A08/S/c.

Other Guidance

- AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. June 2021.[19]

- British Society of Gastroenterology. BSG consensus guidelines on the management of inflammatory bowel disease in adults. 2019.[20]
- ACG Clinical Guideline: Management of Crohn's Disease in Adults. 2018.[21]

Additional Information

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