Health Technology Briefing
October 2024

Apraglutide for treating short bowel syndrome

Company/Developer	Ironwood Pharmaceuticals

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26964	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III/II clinical trials

Summary

Apraglutide is currently in clinical development for the treatment of short bowel syndrome with intestinal failure (SBS-IF) in patients who rely on intravenous parenteral nutrition for essential fluids and nutrients. Short bowel syndrome (SBS) is a condition where part of the small intestine is missing or does not work properly making it hard for the small intestine to digest and absorb the correct amount of nutrients (fats, carbohydrates, vitamins, minerals) or reabsorb fluids. This can happen due to surgical removal to treat intestinal diseases such as Crohn's disease or from birth if the intestine is underdeveloped or malfunctioning. Common symptoms can include diarrhoea, dehydration, malnutrition and unintended weight loss. Patients rely on parenteral nutrition, which is the delivery of specially formulated liquids through a central venous catheter to meet their nutritional or fluid requirements. To improve the quality of life in patients with SBS-IF, there is a need for treatments that reduce dependence on parenteral support.

Apraglutide is a novel long-acting GLP-2 analogue that targets the underlying issue of inadequate absorptive capacity common with SBS. It is designed to increase fluid and nutrient absorption by the remnant intestine of patients who have SBS. It is administered once weekly as a subcutaneous (under the skin) injection. It has the potential to be a potent, selective, and longer-acting treatment which may result in enhanced effect on intestinal growth. If licensed, apraglutide will offer an additional treatment option for adult patients with SBS-IF

Proposed Indication

Adults with short bowel syndrome (SBS) who are dependent on parenteral support.[1]

Technology

Description

Apraglutide is a novel long-acting glucagon-like peptide-2 (GLP-2) analogue that targets the underlying issue of inadequate absorptive capacity common with SBS.[2] Apraglutide is similar to human GLP-2, a hormone made in the gut that increases absorption of nutrients from the intestine. Like GLP-2, apraglutide increases intestinal absorption by increasing blood flow to and from the gut, reducing the speed at which food passes through the gut and reducing acid secretions in the stomach which can interfere with absorption in the intestine.[3] Although human GLP-2 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), apraglutide has increased resistance to DPP-4 breakdown, contributing to its prolonged half-life.[2]

Apraglutide is currently in clinical development for the treatment of patients with short bowel syndrome with intestinal failure (SBS-IF) receiving parenteral support secondary to surgical resection of the small intestine with colon-in-continuity (CIC) or stoma.[4] In the completed pivotal phase III trial (NCT04627025) and ongoing open-label extension trial (NCT05018286), apraglutide is administered once weekly as a subcutaneous (SC) injection.[1,4]

Key Innovation

To improve the quality of life in patients with SBS-IF, there is a need for treatments that reduce dependence on parental support.[5] Treatment with GLP-2 analogues improves intestinal adaptation in patients with SBS intestinal failure (SBS-IF) and may reduce parenteral support requirements.[6] In a preclinical study and a phase I clinical trial, apraglutide has demonstrated early potential to be a potent, selective, and long-acting treatment which may result in enhanced intestinotrophic effect with once-weekly dosing compared to medicines currently available.[7-9] Apraglutide may have a longer-acting nature and is being investigated as a once-weekly SC administration, which may benefit patients more than more frequent administrations.[10]

If licensed, apraglutide will offer an additional treatment option for adult patients with SBS-IF.

Regulatory & Development Status

Apraglutide does not currently have marketing authorisation in the EU/UK for any indication.

Apraglutide is also in phase II clinical development for the treatment of graft versus host disease.[11]

Apraglutide has the following regulatory designations:

- an orphan drug designation in the EU in 2018 for the treatment of SBS.[3]

Patient Group

Disease Area and Clinical Need

SBS occurs when a significant part of the small bowel cannot digest and absorb all the nutrition and fluid they need to maintain health.[12] Patients with SBS-IF need to have parenteral nutrition to meet their nutritional or fluid requirements.[13] SBS can lead to symptoms such as weight loss, malnutrition, diarrhoea and dehydration.[12,14] Causes of SBS include surgical resection due to intestinal disorders such as Crohn's disease, cancer, injuries, blood clots and trauma, as well as being born with some of the small intestine missing or damaged.[15,16] SBS affects males and females in equal numbers.[17]

In the European Union (EU) in 2018, it was estimated that SBS affected approximately 0.6 in 10,000 adults (equivalent to around 31,000 adults).[3] However, the exact incidence and prevalence of SBS in the general population are unknown.[17] Due to the difficulties in determining the incidence and prevalence of SBS, parenteral nutrition is used as a proxy; it is estimated that up to 1,000 people in England have SBS, which requires long-term treatment with parenteral nutrition.[18] In England 2022 – 23, there were 222 finished consultant episodes (FCEs) and 138 admissions for the broad indication 'other intestinal malabsorption' (ICD-10 code K90.8) which resulted in 583 FCE bed days and 75 day cases.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommended treatments for SBS include teduglutide in people aged 1 year or older.[20]

Clinical Trial Information

Trial	**STARS;** NCT04627025, EudraCT2020-001202-32; A Multicenter, Double-blind, Randomized, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Apraglutide in Adult Subjects With Short Bowel Syndrome and Intestinal Failure (SBS-IF). **Phase III** – Active, not recruiting **Location(s):** Ten EU countries, UK, USA, and other countries **Actual study completion date:** January 2024
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N = 164 (actual); subjects with SBS-IF receiving parenteral support secondary to surgical resection of the small intestine with either stoma or colon-in-continuity (CIC)
Intervention(s)	Apraglutide subcutaneous (SC) injections, once weekly
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Relative change from baseline in actual weekly PS volume at week 24 [Time frame: week 24 of treatment]. See trial record for full list of all outcomes
Results (efficacy)	Efficacy results show that the clinical trial met its primary endpoint of relative change from baseline in actual weekly parental support volume at week 24 compared to placebo (-25.5% vs. -12.5%; p=0.001), driven by both stoma and colon-in-continuity subpopulations. Treatment effect with relative parental support volume reduction was observed from week 8 onward (-8% vs -1.6% placebo, p=0.002). Significantly more apraglutide-patients gained additional days off from parenteral support per week at week

	24 versus placebo (≥2 days: 24.5% vs 11.3%, p=0.021; ≥3 days: 11.8% vs 1.9%, p=0.006). Seven apraglutide-treated patients achieved enteral autonomy (three in the stoma subpopulation, four in the colon-in-continuity subpopulation) by week 24 (6.4% apraglutide vs 0% placebo, p=0.006). Three additional colon-in-continuity patients achieved enteral autonomy by week 48: 7/56 [12.5%] apraglutide vs 2/27 placebo [7.4%], p=0.387.[21]
Results (safety)	Apraglutide was well-tolerated, with no new safety signals identified and the safety profile was consistent with previous apraglutide studies.[21]

Clinical Trial Information

Trial	**STARSnutrition;** TA799-013; NCT04964986; A Multicenter, Open-label, Metabolic Balance Study to Evaluate the Effects of Apraglutide on Intestinal Absorption in Adult Subjects With Short Bowel Syndrome, Intestinal Failure (SBS-IF), and Colon-in-Continuity (CIC). **Phase II** – Completed **Location(s):** Two EU countries **Study completion date:** June 2023	**STARS extend,** NCT05018286, EudraCT2020-005513-41; An Open-label Extension Trial to Evaluate the Long-term Safety of Apraglutide in Short Bowel Syndrome. **Phase III** – Active, not recruiting **Location(s):** Ten EU countries, UK, USA and other countries. **Primary completion date**: October 2027
Trial Design	Open label, single group assignment	Single group assignment, open label
Population	N = 9 (actual); subjects with SBS-IF and CIC, receiving parenteral support, secondary to surgical resection of the small intestine; aged 18 years and older	N = 158 (actual); subjects with a diagnosis of SBS-IF secondary to surgical resection of the small intestine, with CIC, or stoma, who were trial subjects of TA-799-007 or TA799-013; aged 18 years and older
Intervention(s)	Apraglutide SC injections, once weekly	Apraglutide SC injections, once weekly
Comparator(s)	None	None
Outcome(s)	Primary outcome measures: • To evaluate the safety and tolerability of apraglutide [Time frame: from baseline to week 48] See trial record for full list of other outcomes	Primary outcomes: • Adverse event [Time frame: from baseline to week 208] • Clinical chemistry [Time frame: from baseline to week 208] • Hematology [Time frame: from baseline to week 208] • Hemostasis [Time frame: from baseline to week 104] • Urinalysis [Time frame: from baseline to week 208]

		• Occurrence of clinically relevant changes in vital signs [Time frame: from baseline to week 208] • Occurrence of clinically relevant changes in electrocardiogram [Time frame: from baseline to week 208] See trial record for full list of other outcomes
Results (efficacy)	Apraglutide improved intestinal absorption as indicated by 50% parenteral support (PS) volume and energy content decrease, resulting in one or more days off PS. PS reduction was observed as early as week four and was maintained until the end of the study. Seventy-eight percent (78%) of patients gained one or more days off PS with all patients achieving clinical response.[22]	-
Results (safety)	Apraglutide had an acceptable safety profile and appeared well tolerated in the STARS Nutrition trial, which was the primary study objective.[22]	-

Clinical Trial Information

Trial	NCT03415594; A Once-weekly, Repeated Dose, Placebo Controlled, Double Blind, Randomised Cross-over Trial Investigating Safety, Efficacy and Pharmacodynamics of apraglutide in Patients With Short Bowel Syndrome With Intestinal Failure Requiring Parenteral Support Followed by an Additional Treatment Period in an Open Label Regimen. **Phase I & II** – Completed **Location(s):** Denmark **Study completion date**: November 2019
Trial Design	Randomised, crossover assignment, triple masking
Population	N=8 (actual); adult subjects with short bowel syndrome who require total parenteral nutrition; aged 18 to 80 years old
Intervention(s)	Apraglutide (FE203799 GLP-2 analogue) 5mg once weekly SC administration
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Incidence of treatment-emergent adverse events [Time frame: day 28 to day 29] See trial record for full list of other outcomes.

Results (efficacy)	Change from baseline in urine volume output was a secondary efficacy outcome. Treatment with once-weekly 5 and 10mg apraglutide doses significantly increased urine volume output by an adjusted mean of 714 ml/day (95% CI, 490-939; *P* <.05) and 795ml/day (95% CI, 195-1394; *P* <.05), respectively, compared with placebo, with no significant differences between doses.[23]
Results (safety)	Common treatment-related adverse events (AEs) were mild to moderate and included polyuria, decreased stoma output, stoma complications, decreased thirst, and edema. No serious AEs were likely to be related to apraglutide treatment. The safety profile was comparable for the lower and higher doses.[23]

Clinical Trial Information

Trial	NCT03408132; A Phase Ib/IIa Open-label, Repeated Dose, Metabolic Balance Study of apraglutide in Patients With Short Bowel Syndrome and Intestinal Insufficiency. **Phase I & II** – Completed **Location(s)**: Denmark **Study completion date**: October 2019
Trial Design	Single group assignment, open label
Population	N = 8 (actual); males and females with SBS secondary to surgical resection of the small intestine, with or without an intact colon; aged 18 to 80 years.
Intervention(s)	Apraglutide (FE203799) 5 mg SC injection
Comparator(s)	None
Outcome(s)	Primary outcome: Incidence of treatment-emergent adverse events [Time frame: day 28 to day 26 plus 6 weeks]. See trial record for full list of other outcomes.
Results (efficacy)	Apraglutide significantly increased wet weight and energy absorption by an adjusted mean of 741 g/day (95% CI, 194 to 1287; *P* = 0.015) and 1095 kJ/day (95% CI, 196 to 1994; P = 0.024), respectively. Sodium and potassium absorption significantly increased by an adjusted mean of 38 mmol/day (95% CI, 3 to 74; *P* = 0.039) and 18 mmol/day (95% CI, 4 to 32; *P* = 0.020), respectively.[2]
Results (safety)	Common treatment-related AEs were decreased gastrointestinal (GI) stoma output (n = 6), stoma complications (n = 6), GI stoma complications (n = 5), nausea (n = 5), flatulence (n = 4), abnormal GI stoma output (n = 4), polyuria (n = 3), and abdominal pain (n = 3). The only treatment-related serious AE (experienced in one patient) was abdominal pain.[2]

Estimated Cost

The cost of apraglutide is not yet known.

Relevant Guidance

NICE Guidance
• NICE technology appraisal. Teduglutide for treating short bowel syndrome (TA804). June 2022
NHS England (Policy/Commissioning) Guidance
• NHS England. August 2023. NHS Service Specification. Severe Intestinal Failure (Adults). 170077S – 230701S. • NHS England. December 2018. Small Bowel transplantation service (children and adults). • NHS England. 2013/14 NHS Standard Contract for Autologous Intestinal Reconstruction Service (Adult). A08/A(HSS)a.
Other Guidance
• Bering J, DiBaise J, Short bowel syndrome: Complications and management. 2023.[24] • Iyer K, DiBaise JK, Rubio-Tapia A. AGA Clinical Practice Update on Management of Short Bowel Syndrome: Expert Review. 2022.[25] • DiBaise JK, Parrish C. Managing the Adult Patient With Short Bowel Syndrome. 2017.[26] • British Society of Gastroenterology. Guidelines for the management of patients with a short bowel. 2006.[27]

Additional Information

Ironwood Pharmaceuticals did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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