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HEALTH TECHNOLOGY BRIEFING
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Pexidartinib for tenosynovial giant cell tumour

NIHRIO ID	23830	**NICE ID**	9867
Developer/Company	Daiichi Sankyo Ltd	**UKPS ID**	652897

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Pexidartinib is a medicinal product that is being developed for the treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT). TGCT is also referred to as giant cell tumour of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS). TGCT is a rare, neoplasm derived from the thin layer of tissue that lines the joints and tendons leading to the formation of a mass. TGCT normally affects young adults of both sexes and is associated with severe morbidity and functional limitation. Surgery is currently the standard treatment although some cases of TGCT have a poorer likelihood of successful cure with surgery due to the high risk of recurrence. There are no current systemic treatment for symptomatic TGCT.

Pexidartinib belongs to a group of medicines known as tyrosine kinase inhibitors (TKI). It is given orally as a capsule and works by blocking a receptor called colony-stimulating factor-1 receptor (CSF1R) to which a protein called macrophage colony-stimulating factor (M-CSF) attaches. By attaching and blocking CSF1R, pexidartinib is expected to block the activity of M-CSF, preventing tumour growth and helping to delay the onset of the symptoms of the disease. If licensed, pexidartinib may offer the first systemic treatment option for adults with symptomatic TGCT which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

PROPOSED INDICATION

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

Treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), also referred to as giant cell tumour of the tendon sheath (GCT-TS) or pigmented villonodular synovititis (PVNS), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.[a]

TECHNOLOGY

DESCRIPTION

Pexidartinib (PLX3397) is a novel, orally active small-molecule tyrosine kinase inhibitor (TKI) that targets colony stimulating factor 1 receptor (CSF1R). It also inhibits the KIT proto-oncogene receptor tyrosine kinase and the FMS-like tyrosine kinase 3 (FLT3) harbouring an internal tandem duplication.[1] Pexidartinib is the most advanced selective CSF-1R inhibitor under clinical development. In preclinical studies, pexidartinib inhibited the proliferation of cell lines that depend on CSF1R at a concentration below 1 µmol/L. Ligand-induced autophosphorylation of CSF1R is also inhibited by pexidartinib.[1,2]

Pexidartinib is in clinical development for the treatment of symptomatic TGCT and is currently in phase III clinical trial (ENLIVEN; NCT0237169).[3] The recommended dose of pexidartinib is 400 mg (2 × 200 mg hard capsules) taken twice daily (BID) on an empty stomach (at least 1 hour before or 2 hours after a meal). In part one of the Phase III ENLIVEN study, 1000 mg pexidartinib was administered per day orally (400 mg morning; 600 mg evening) for the first 2 weeks, followed by 800 mg per day (400 mg twice a day) for 22 weeks. In part two of the Phase III ENLIVEN study, patients received open-label pexidartinib at the dose of pexidartinib or placebo they were receiving at the end of part one.[4]

INNOVATION AND/OR ADVANTAGES

Currently, no systemic antitumor agents are approved for the treatment of TGCT.[1] Pexidartinib is the only agent that is being assessed in a phase III randomised trial for the treatment of TGCT, which has shown encouraging results on overall response and rate of disease control.[1] Responses were also associated with an improved joint function and reduced pain.[5]

Initial results from the ongoing phase III clinical trial suggest that pexidartinib achieved a high tumour response with an improved clinical response.[1,4] With continued pexidartinib treatment, the tumour response rate increased to 53% according to RECIST, and the tumour volume decreased by 50% or more in 64% of patient. Reduction in the tumour was associated with clinically meaningful improvement in function and disease symptoms assessed by a wide range of relevant quality-of life endpoints.[1]

Taking into account the severe morbidity (pain, stiffness and reduced range of motion), poor quality of life with TGCT and the limitations of available treatment when the disease is not amenable to surgery, pexidartinib as a selective CSF1R TKI may offer the first systemic treatment option for patients suffering from TGCT with severe morbidity or functional limitations and for whom no proven treatment options exist.[1,4]

[a] Information provided by Daiichi Sankyo UK Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pexidartinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Pexidartinib has the following regulatory designations/awards

- An orphan drug in the EU in March 2015 for the treatment of TGCT, localised and diffuse type.[6]
- Breakthrough therapy by the US FDA for TGCT in November 2015.[7]
- Priority Review by the US FDA Treatment of TGCT in February 2019.[8]
- FDA approval for the treatment of select patients with TGCT in August 2019.[9]

PATIENT GROUP

DISEASE BACKGROUND

Tenosynovial giant cell tumour (TGCT) is a rare, benign neoplasm arising from the synovial lining of joints, bursae or tendon sheaths, predominately affecting young adults (<40 years) of both sexes.[10-12] It occurs in two forms, the localised-form and diffuse-type, which are renamed by the World Health Organisation (WHO) to giant cell tumour of the tendon sheath (GCT-TS) and diffuse-type pigmented villonodular synovitis (PVNS) respectively.[5,12,13] Currently, there is still disagreement on the nomenclature of these diseases, and a new WHO classification is in preparation.[5] The localised form is most common and generally follows an indolent course, frequently affecting the tendon sheath, joints of hands and ankle/foot.[14,15] In contrast, diffuse-type TGCT are less common and mainly affect the knee, hip or shoulder.[15]

Although not life-threatening, TGCT can disrupt daily living and adversely alter an individual's life trajectory.[16] Clinical presentation of TGCT is highly variable and symptoms initially are minimal due to the slowly progressive nature of the disease. Localised TGCT can present with locking or clicking sensations of the affected joints, while the diffuse disease is relatively painless and can cause slight discomfort and swelling.[1,5] However, as the tumour mass grows and gradually expands within the intra- and extra-articular space, symptoms such as pain, swelling, tenderness and reduced ROM of the affected joint can become severe, resulting in functional limitations and poorer quality of life in young adults.[1,17] The exact causes and risk factors for developing TGCT are unknown.[18]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-2018, there were 447 finished consultant episodes (FCE) for TGCT or PVNS (ICD-10 code: M12.2), 441 hospital admissions, resulting in 388 FCE bed days and 237 day cases.[19] TGCT affects adults predominantly between 20-50 years with equal sex prevalence.[5] In England, mean age reported in 2017-2018 was 40 years.[19] Global incidence rates reported based on the Dutch Pathology Registry (PALGA) were 10 per 1,000,000 person-years for GCT-TS and 4 per 1,000,000 person-years for Dt-GCT.[5]

While based on a cohort study in Denmark reported a prevalence rate of 44.3 and 11.5 per 1,000,000 people for GCT-TS and Dt-GCT respectively. The annual incidence rate for TGCT overall has been estimated at 11 cases per 1,000,000 in the United States, including 9.2 localised and 1.8 diffuse cases per 1,000,000.[5]

Incidence and prevalence rates are low due to the rare nature of the disease and party due to unfamiliarity of doctors with the disease which would probably lead to the underreporting and underdiagnosing of TGCT.[5,20,21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment options for TGCT include surgical resection, radiation therapy, immunotherapy and targeted therapy or combination of these methods.[22-24] However, surgical resection, when feasible, is the standard treatment for TGCT which depends upon clinical and radiological presentation of the disease.[4,24,25]

Surgical options for TGCTs include a partial or total synovectomy using arthroscopic and open techniques. A localised disease is readily curable with arthroscopic and open techniques and rarely recurs after marginal surgical excision with recurrence rate below 10%. However, the diffuse disease has shown high rates of recurrence of 40% and is more difficult to treat with surgical resection (arthroscopic and open techniques) alone so that adjuvant therapies are often used.[4,26]

CURRENT TREATMENT OPTIONS

No current systemic treatments are available for this indication.[1]

PLACE OF TECHNOLOGY

If licensed, pexidartinib will offer the first systemic treatment option for adults with symptomatic TGCT associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

CLINICAL TRIAL INFORMATION

Trial	**ENLIVEN, NCT02371369 , EudraCT2014-000148-14, PLX108-10 pexidartinib vs placebo, phase III**
Sponsor	Daiichi Sankyo Ltd
Status	Ongoing
Source of Information	Trial registry[3], manufacturer[1], publication[4]
Location	EU (incl UK), USA, Canada and Australia
Design	Randomised, placebo-controlled; double-blind, parallel assignment
Participants	n=120; aged 18 years and older; diagnosis of PVNS or GCT-TS; measurable disease of at least 2 cm and otherwise based on RECIST 1.1; symptomatic disease because of PVNS or GCT-TS; stable prescription of analgesic regimen during the 2 weeks prior to randomisation; during the 2 weeks prior to randomisation, at least 4 of 7 consecutive days of Brief Pain Inventory (BPI), Worst Pain NRS items and Worst Stiffness NRS items completed correctly.
Schedule	Part 1: participants were randomised to: • pexidartinib, 1000 mg (5 capsules/day) for 2 weeks, then 800 mg (4 capsules/day) for 22 weeks • matching placebo (5 capsules/day) for 2 weeks and then matching placebo (4 capsules per day) for 22 weeks Part 2 • Participants received pexidartinib in part 1 and in part 2 at their prescribed dose

	• Participants received placebo in part1 and pexidartinib in part 2 at their prescribed dose
Follow-up	Estimated follow-up of 46 months
Primary Outcomes	• Percentage of participants achieving complete or partial response at week 25 (based on centrally read MRI scans and RECIST 1.1.) • Percentage of participants achieving complete or partial response by the end of the trial at 46 months (based on centrally read MRI scans and RECIST 1.1.)
Secondary Outcomes	• Patient-Reported Outcome (PRO); Physical Function- (Time frame to the end of the trial at 46 months) • PRO: Worst Pain (Time frame to the end of the trial at 46 months) • PRO: Worst Stiffness (Time frame to the end of the trial at 46 months) • Percentage of the participants achieving complete or partial response based on Tumour Volume Score (Time frame: to the end of the trial at 46 months) • Mean range of motion (ROM) at 46 months (Time frame to the end of the trial at 46 months) • Duration of response at 46 months (Time frame to the end of the trial at 46 months)
Key Results	• The study met its primary endpoint of tumour response rate at week 25. The overall response rate (ORR) was 39.3% (95% CI: 28.1%, 51.9%) for pexidartinib versus 0 (95% CI: 0.0, 6.1%) for placebo (P < 0.0001) The primary endpoint reflected a substantial reduction in tumour size • The study also met the first four of its secondary endpoints of joint ROM, TVS, and PROs of physical function and stiffness, demonstrating statistically significant results versus placebo
Adverse effects (AEs)	Serious adverse events occurred in eight (13%) of 61 patients in the pexidartinib group and one (2%) of 59 in the placebo group. Hair colour changes (67%), fatigue (54%), aspartate aminotransferase increase (39%), nausea (38%), alanine aminotransferase increase (28%), and dysgeusia (25%) were the most frequent pexidartinib-associated adverse events (any grade).
Expected reporting date	Estimated primary completion date reported as December 2019. Estimated study completion date reported as April 2022.

ESTIMATED COST

The cost of pexidartinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

No other relevant guidance identified

ADDITIONAL INFORMATION

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