Health Technology Briefing
November 2024

Repotrectinib for treating neurotrophic tyrosine receptor kinase fusion-positive solid tumours

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 39122	NICE ID: Not available	UKPS ID: 668001

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Repotrectinib is currently in clinical development for treating Neurotrophic Tyrosine Receptor Kinase (NTRK) fusion-positive solid tumours. NTRK fusion-positive solid tumours are a type of cancer characterised by the presence of a fusion between the NTRK gene and another unrelated gene. This fusion leads to the production of an abnormal protein that can drive cancer growth. These tumours can occur in a variety of solid tumour types, including breast, colorectal, lung, thyroid, and salivary gland cancers, among others. Older therapies for NTRK fusion-positive tumours faced issues like resistance mutations, limited effectiveness against brain metastases, shorter response durations, and side effects impacting quality of life.

Repotrectinib is a type of targeted therapy. It identifies and attacks specific types of cancer cells while causing less damage to normal cells, which may be more effective than current standard treatments. Repotrectinib is administered orally. If licensed, repotrectinib will offer an additional treatment option with greater effectiveness and fewer side effects for patients with NTRK fusion-positive solid tumours.

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.

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Proposed Indication

Treatment for adult and paediatric patients 12 years of age and older with advanced solid tumours harbouring NTRK1-3 rearrangements[1]

Technology

Description

Repotrectinib (AUGTYRO, TPX-0005) is a small (low molecular weight), macrocyclic tyrosine kinase inhibitor of ROS1 and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, TRKC, and anaplastic lymphoma kinase (ALK). Repotrectinib was designed to efficiently bind with the active kinase conformation and avoid steric interference from a variety of clinically resistant mutations.[2,3]

Oral repotrectinib is currently in clinical development (NCT03093116) for advanced solid tumours harbouring ALK, ROS1, or NTRK1-3 rearrangements.[1] On the basis of the dose escalation from the phase 1 trial, the recommended phase 2 dose of repotrectinib was 160 mg daily for 14 days, followed by 160 mg twice daily.[4]

Key Innovation

Repotrectinib has a compact macrocyclic structure that enhances its binding affinity, allowing for potent inhibition of both wild-type and resistant mutant forms of tropomyosin receptor kinase (TRK) proteins. This feature is critical as it addresses the common challenge of resistance mutations that arise during treatment with first- and second-generation inhibitors, which often struggle to effectively target these altered kinases. The ability of repotrectinib to maintain efficacy in TKI-naïve patients and those with prior treatment failures further underscores its potential as a second-line therapy.[5,6] Furthermore, Older therapies for NTRK fusion-positive tumours faced issues like resistance mutations, limited effectiveness against brain metastases, shorter response durations, and side effects impacting quality of life.[7] If licensed, repotrectinib will offer an additional treatment option with greater effectiveness and fewer side effects for patients with NTRK fusion-positive solid tumours.

Regulatory & Development Status

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

Repotrectinib is in phase II/III clinical development for:[8]

- Non-small cell lung cancer
- Brain metastases
- Locally advanced solid tumors
- Metastatic solid tumors
- Lymphoma
- Primary central nervous system (CNS) tumors
- Advanced cancer

Repotrectinib has the following regulatory designations/awards:[9,10]

- Fast Track designation by Food and Drug Administration (FDA) for NTRK-positive advanced solid tumors in August 2020

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Patient Group

Disease Area and Clinical Need

The tropomyosin receptor kinase (TRK) family of proteins is encoded by NTRK genes and has a role in the development and normal functioning of the nervous system, such as the regulation of pain, thermoregulation, movement, memory, appetite, and cognition. Gene fusions involving NTRK1, 2, or 3 (encoding the neurotrophins receptors TRKA, B, and C, respectively) have been identified in several solid tumour types arising in patients and can be detected in the clinic using tumour DNA and RNA sequencing. Solid tumours are defined as abnormal masses of tissue that usually do not contain cysts or liquid areas and may be benign or malignant. Some solid tumours may be caused by specific genetic changes, for example, mutation in the NTRK genes, which can affect signalling inside the cell which drives cell growth and cause an uncontrolled increase of cancer cells. These gene mutations are rare, hence the need for effective therapies that can target gene alterations shared by multiple tumour types regardless of site of origin.[11] Laboratory evidence and clinical evidence suggest that NTRK gene fusions are oncogenic drivers of various adult and paediatric tumour types and predictive biomarkers for targeted inhibition.[12]

NTRK gene fusions are associated with a variety of cancers like breast cancer, colorectal cancer, lung cancer, thyroid cancer, etc. Although rare in common solid tumours, with a frequency of <1%, NTRK gene fusions occur more frequently in some rare tumour types, for example, <5% in lung and colorectal cancers, 5%-25% in thyroid cancer, and >90% in secretory carcinoma of salivary gland.[13] The population likely to be eligible to receive repotrectinib could not be estimated from available published sources. However, in England in 2023-2024 there were 12,353 finished consultant episodes (FCE) and 8,343 hospital admissions for malignant neoplasm without specification of site (ICD-10 codes C80), resulting in 44,251 FCE bed days and 4,299 day cases for this condition.[14]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) has recommended the use of Larotrectinib for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children if:[15]

- the disease is locally advanced or metastatic or surgery could cause severe health problems and
- they have no satisfactory treatment options.

It is recommended only if the conditions in the managed access agreement for larotrectinib are followed.

- his recommendation is not intended to affect treatment with larotrectinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person or their parents or carers.

Clinical Trial Information

Trial	**TRIDENT-1**; NCT03093116; EudraCT 2016-003616-13; A Phase 1/2, Open-Label, Multi-Centre, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumour Activity of TPX-0005 in Patients With Advanced Solid Tumours Harbouring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1) **Phase I/II** – Recruiting

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	Location(s): 9 EU countries, UK, USA, Canada, and other countries **Primary completion date:** Feb 2028
Trial Design	Single group assignment, open label
Population	N=500; patients 12 years and older; histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumour that harbours an ALK, ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement by protocol specified tests
Intervention(s)	Oral repotrectinib
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Dose limiting toxicities (DLTs) (Phase 1) [time frame: Within 28 days of the first repotrectinib dose] • Recommended Phase 2 Dose (RP2D) (Phase 1) [time frame: Within 28 days of the last patient dosed in escalation] • Overall Response Rate (ORR) Phase 2 [time frame: Two to three years after first dose of repotrectinib dose] See trial record for full list of other outcomes
Results (efficacy)	Median number of prior TKI treatment was 1 (0-3) with all of TKI naïve and 83% of TKI pre-treated patients (pts) received prior chemotherapy. Among 10 evaluable TKI-naïve ROS1+ NSCLC patients, confirmed ORR by Blinded Central Review (BCR) was 90% (95% CI 56 - 100) with median duration of response (DOR) not reached ((range 5.5+ – 14.9+ months (months, mo)). Among 18 TKI pretreated patients, confirmed ORR by BCR was 28% (95% CI 10 – 54) with DOR of 10.2 mos. Subgroup analysis showed confirmed ORR 44% (95% CI 14 - 79) in 9 prior TKI pts and treated at dose levels of 160 mg daily or above. In 7 pts with measurable target CNS lesions at baseline, the intracranial ORR was 3/3 (100%) with DOR (5.5+; 7.2+; 14.85+ mos) in TKI-naïve patients and 2/4 (50%) with DOR (5.5+;14.8+, mo) in TKI-pretreated patients, respectively.[16]
Results (safety)	Most AEs (adverse events) were manageable and grade (Gr) 1-2. Common (>20%) treatment-related AEs were dizziness (49%), dysgeusia (48%), paraesthesia (28%), and constipation (20%). Four dose limiting toxicities (Gr3 dyspnoea/hypoxia (n = 1); Gr2 (n = 1) and Gr3 (n = 1) dizziness at 160 mg twice daily, and Gr3 dizziness (n = 1) at 240 mg daily) occurred and were managed with dose modifications.[16]
Clinical Trial Information	
Trial	NCT04094610; EudraCT 2019-003055-11; A Phase 1/2, Open-Label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumour Activity Study of Repotrectinib in Paediatric and Young Adult Subjects With Advanced or Metastatic Malignancies Harboring ALK, ROS1, NTRK1-3 Alterations **Phase I/II** – Recruiting **Location(s):** 4 EU countries, UK, USA, Canada, and other countries **Primary completion date:** Sep 2026
Trial Design	Single group assignment, open label

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Population	N=75; 12 years and older (up to 25 Years); confirmed diagnosis of genetic ROS1 point mutation, fusion, or amplification or NTRK1-3 fusion
Intervention(s)	Capsules or oral suspension repotrectinib
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Dose limiting toxicities (DLTs) (Phase 1) [Time Frame: Within 28 days of the first repotrectinib dose] • Paediatric Recommended Phase 2 Dose (RP2D) (Phase 1) [Time Frame: Within 28 days of the last patient dosed in escalation] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of repotrectinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Larotrectinib for treating NTRK fusion-positive solid tumours (TA630). May 2020.
- NICE technology appraisal guidance. Entrectinib for treating NTRK fusion-positive solid tumours (TA644). August 2020.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- European Society of Medical Oncology (ESMO). ESMO Guideline. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. 2019.[17]
- Schram, A., Chang, M., Jonsson, P. et al. Fusions in solid tumours: diagnostic strategies, targeted therapy, and acquired resistance. 2017.[18]

Additional Information

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