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HEALTH TECHNOLOGY BRIEFING DECEMBER 2020

Plinabulin in combination with G-CSF for chemotherapy-induced neutropenia

NIHRIO ID	23905	**NICE ID**	10496
Developer/Company	BeyondSpring Pharmaceuticals Inc.	**UKPS ID**	Not available

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

SUMMARY

Plinabulin in combination with G-CSF is being developed for the prevention of chemotherapy-induced neutropenia (CIN) in patients with solid tumours receiving myelosuppressive chemotherapy with docetaxel, doxorubicin, and cyclophosphamide (TAC). Neutropenia is a condition associated with low levels of neutrophils, a type of white blood cell, which is a common side effect of cancer treatment. Severe neutropenia can lead to life-threatening complications due to resulting infections, and cause reduction or delay of chemotherapy treatment, potentially compromising the benefit to cancer patients.

Plinabulin (administered intravenously (IV)) has both anti-cancer and neutropenia-prevention effects. It binds to and affects the function of the protein, tubulin, within body cells, ultimately leading to cancer cell death. Plinabulin also boosts the number of cells in the bone marrow that are the source of mature immune cells in the blood, including neutrophils. If licensed, plinabulin in combination with G-CSF will offer an additional treatment option for preventing CIN in patients with solid tumours receiving myelosuppressive chemotherapy with TAC.

PROPOSED INDICATION

Prevention of CIN in patients with solid tumours receiving myelosuppressive chemotherapy with docetaxel, doxorubicin, and cyclophosphamide (TAC).[1-4]

TECHNOLOGY

DESCRIPTION

Plinabulin (BPI-2358) is a synthetic, marine-derived, low molecular weight, new chemical entity that belongs to the diketopiperazine class of compounds. It is a non–granulocyte colony-stimulating factor (G-CSF) small molecule with both anti-cancer and neutropenia-prevention effects. Plinabulin reversibly binds to β-tubulin within the colchicine pocket, preventing polymerisation into microtubules. Following microtubule disruption, plinabulin exerts diverse cellular effects ranging from direct killing of cancer cells and proliferating endothelial cells, to increasing dendritic cell maturation. [1,5-7]

Plinabulin is currently in clinical development for the treatment of CIN in patients with solid tumours receiving TAC. In the phase III clinical trial (Protective 2, NCT03294577), patients received TAC on Day 1 every 21 days, 40 mg plinabulin (administered via IV infusion) 30 minutes after the end of the TAC, and 6 mg of pegfilgrastim on Day 2 of each cycle (≥24 hours after completing chemotherapy).[1]

INNOVATION AND/OR ADVANTAGES

The current treatment for myelosuppressive chemotherapy calls for the prophylactic administration of G-CSF-based therapies such as a longer acting pegylated form of G-CSF. The prophylactic use of G-CSF agents has limitations in terms of cost, convenience of use, and adverse effects.[6] In tumour cells, disrupting microtubules with plinabulin reduces cell proliferation and causes cell suicide, including in KRAS wild type and KRAS mutant cancer cells. In addition to anti-cancer benefits, clinical and nonclinical testing has demonstrated a dramatic positive effect of plinabulin on CIN. Plinabulin boosts the number of primitive stem/progenitor cells in the bone marrow that are the source of mature immune cells in the blood, including neutrophils. The effect of microtubule targeting on stem/progenitor cell number may therefore significantly contribute to the anti-CIN benefits of plinabulin.[5]

The mechanism underlying the anti-CIN benefits of plinabulin is distinct from the standard of care for CIN, G-CSF based therapeutics. Plinabulin shows evidence of alleviating chemotherapy induced thrombocytopenia and near prevention of bone pain caused by G-CSF based therapy.[5] Importantly, plinabulin significantly reduced CIN in cancer patients when administered within 1 hour following treatment with another tubulin-targeted therapy, docetaxel. It can be administered shortly after chemotherapy and therefore is more convenient to patients who would not need to return to hospital on day 1 – 3 post chemotherapy for anti-CIN treatment.[6]

In the phase III clinical trial, plinabulin in combination with pegfilgrastim showed a statistically significant improvement compared to pegfilgrastim alone in the rate of prevention of Grade 4 neutropenia with a lower reported adverse event (AE) frequency (58.6%) for combination therapy compared to 80.0% in pegfilgrastim monotherapy.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Plinabulin is also currently in phase II/III clinical developments for non-small cell lung cancer.[9]

Plinabulin was awarded the Breakthrough Therapy Designation by the US FDA and China's Centre for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) for the CIN indication in September 2020.[10]

PATIENT GROUP

DISEASE BACKGROUND

Neutropenia (neutropenic sepsis or febrile neutropenia) is defined as a decrease in the absolute number of neutrophils, also called absolute neutrophil count (ANC), in the blood.[11] Myelosuppression is the primary toxicity of many chemotherapy regimens, and neutropenia in particular is a frequent and potentially life-threatening complication.[6] Neutropenia is mostly associated with chemotherapy and radiotherapy.[11]

Chemotherapies deplete proliferating cells in the bone marrow, leading to a reduction in blood absolute neutrophil count that can occur in a matter of days due to the short half-life of circulating mature neutrophils.[6] Although neutropenia is common during chemotherapy, severe neutropenia is not and can cause serious morbidity and mortality due to resulting infections.[11] Patients that develop severe neutropenia are more susceptible to hospitalisation and potentially fatal infections, with a risk for febrile neutropenia (neutropenia with fever) that increases with neutropenia severity and duration. Furthermore, severe neutropenia often necessitates omitting scheduled chemotherapy administrations, potentially compromising the benefit to cancer patients.[6]

Neutropenia incidence is mainly and highly associated with the first cycle of the chemotherapy more than the other or subsequent cycles.[11] Risk factors for the development of neutropenia in cancer patients include older age, comorbidities, poor performance status, advanced disease, low baseline blood cell counts, and low body surface area/body mass index and specific genetic polymorphisms.[12,13] People with a lowered immune system from other causes, such as having human immunodeficiency virus (HIV) or an organ transplant, are also more likely to develop neutropenia.[14]

Neutropenia itself may not cause any symptoms. People usually find out they have neutropenia from a blood test or when they get an infection. Signs of infection include:[14,15]

- A fever of 38°C or higher
- Chills or sweating
- Sore throat, sores in the mouth, or a toothache
- Abdominal pain
- Pain near the anus
- Pain or burning when urinating, or urinating often
- Diarrhoea or sores around the anus
- A cough or shortness of breath
- Skin rashes and any redness, swelling, or pain (especially around a cut, wound, or catheter)
- Unusual vaginal discharge or itching
- Flu-like symptoms

Neutropenia has a dramatic and detrimental effect on the patients' quality of life. Fatigue is the predominant characteristic, which leads to a decrease in the ability to perform daily life activities. Patients describe fatigue as feeling weak and exhausted. Psychological problems

were also reported by the patients, such as sadness, anxiety, reduced self-worth, and inability to fulfil normal roles.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Neutropenia generally occurs in one out of three patients treated with chemotherapy.[11] In March 2020 there were 517,963 known cases of all types of cancer in the UK.[16] In England in 2013-2014, 28.4% of patients received chemotherapy as part of their primary treatment.[17] Therefore, it can be estimated that around 147,101 people will receive chemotherapy. Mortality rates of neutropenic sepsis ranges between 2% and 21% have been reported in adults.[18]

The reported incidence of CIN varies widely, with reports ranging from 6 – 50% of patients depending on the cancer type, disease staging, patient functional status and chemotherapy regimen.[19] Using these figures, we can estimate between 8,826 and 73,550 people in the UK may experience CIN.

The ICD-10-CM code D70 is used to classify a condition called agranulocytosis, which includes drug-induced neutropenia.[20] The 2019-2020 Hospital Episodes Statistics for England recorded a total of 10,273 finished consultant episodes (FCE) for agranulocytosis, resulting in 8,160 hospital admissions and 25,906 FCE bed days and 1,658 day cases.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

For adult patients (aged 18 years and older) with acute leukaemia, stem cell transplants or solid tumours in whom significant neutropenia is an anticipated consequence of chemotherapy, patients are offered prophylaxis with a fluoroquinolone during the expected period of neutropenia only. Rates of antibiotic resistance and infection patterns should be monitored in treatment facilities where patients are having fluoroquinolones for the prophylaxis. G-CSF should not be routinely offered for the prevention of neutropenia in adults receiving chemotherapy unless the patients are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity.[22]

If the patient is neutropenic, intravenous fluids, antibiotic therapy and all prescribed medical treatment must be commenced immediately.[23] In secondary and tertiary care, neutropenia is treated as an acute medical emergency and therefore patients are offered empiric antibiotic therapy immediately. Inpatient empiric antibiotic therapy in all patients who have unresponsive fever should be continued, unless an alternative cause of fever is likely. Empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count, should be discontinued.[22]

CURRENT TREATMENT OPTIONS

According to the National Institute of Health and Care Excellence (NICE), beta lactam monotherapy with piperacillin with tazobactam is recommended as initial empiric antibiotic therapy to patients with suspected neutropenia who need intravenous treatment.[18,24]

PLACE OF TECHNOLOGY

If licensed, plinabulin in combination with G-CSF will offer an additional treatment option for preventing CIN in patients with solid tumours receiving myelosuppressive chemotherapy with TAC.

CLINICAL TRIAL INFORMATION

Trial	**Protective 2; BPI-2358-106 Phase 3;** NCT03294577; A Phase 3, Randomized Study to Evaluate Plinabulin Versus Pegfilgrastim in the Prevention of Severe Neutropenia in Breast Cancer Patients Receiving Myelosuppressive Chemotherapy With Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) (Protective 2) **Phase III –** active, not recruiting **Location(s):** China and Ukraine **Primary completion date:** October 2020
Trial design	Randomised, parallel assignment, triple-blinded
Population	N=222; female patients who are candidates for adjuvant or neoadjuvant TAC with biopsy-proven, early stage (Stage I and II) and Stage III breast cancer, and have not had prior chemotherapy; aged 18 years and older
Intervention(s)	Patients were administered: • Cycles 1 to 4 consist of TAC (or TC for Cycles 2 to 4) administered IV on Day 1 every 21 days • Single dose of 40 mg plinabulin (IV) in a double blinded manner, 30 minutes after the end of the TAC (or TC for Cycles 2 to 4) infusion • 6 mg of pegfilgrastim (subcutaneous) on Day 2 of each cycle (≥24 hours after completing chemotherapy)
Comparator(s)	Patients were administered: • Cycles 1 to 4 consist of TAC (or TC for Cycles 2 to 4) administered IV on Day 1 every 21 days • 250 ml D5W placebo matching plinabulin (IV) over 30 minutes (±5 minutes) in a double blinded manner, 30 minutes after the end of the TAC (or TC for Cycles 2 to 4) • 6 mg pegfilgrastim (subcutaneous) on Day 2 of each cycle (≥24 hours after completing chemotherapy)
Outcome(s)	Primary outcome: Percentage of patients with duration of severe neutropenia (DSN) =0; assessed by days of Grade 4 neutropenia (ANC< 0.5 × 109/L) [Time frame: duration of Grade 4 neutropenia assessed during the first cycle (21 days)] See trial record for full list of other outcomes
Results (efficacy)	Plinabulin in combination with pegfilgrastim showed a statistically significant improvement compared to pegfilgrastim alone in the rate of prevention of Grade 4 neutropenia in Cycle 1, as well as achieving statistical significance in all key secondary endpoints, including duration of severe neutropenia (DSN) and absolute neutrophil count (ANC) nadir:[8]

	• Grade 4 neutropenia in Cycle 1: 31.5% combination therapy vs. 13.6% pegfilgrastim monotherapy, 95% CI 17.90 (7.13, 28.66), p=0.0015) • DSN Cycle 1 Day 1-8 (ANC < 0.5 x 10^9 cells/L), p=0.0065 • DSN Cycle 1: p=0.03 • Mean ANC nadir Cycle 1 (x 10^9 cells/L): p=0.0002 • Duration of profound neutropenia Cycle 1 (ANC< 0.1 x 10^9 cells/L): p=0.0004
Results (safety)	Lower Grade 4 adverse event (AE) frequency (58.6%) for combination therapy compared to 80.0% in pegfilgrastim monotherapy.[8]

Trial	**Protective-1; BPI-2358-105 Phase 3;** NCT03102606; A Phase 3, Multicenter, Randomized, Double Blind, Study to Evaluate Duration of Severe Neutropenia With Plinabulin Versus Pegfilgrastim in Patients With Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy (Protective 1) **Phase III –** active, not recruiting **Location(s):** USA, China, Russian Federation and Ukraine **Primary completion date: November** 2020
Trial design	Randomised, parallel assignment, triple-blinded
Population	N=150; adult patients with advanced or metastatic breast cancer, who have failed >/= 1 but < 5 prior lines of chemotherapy; locally advanced or metastatic non-small cell lung cancer (NSCLC) after platinum therapy failure; or hormone refractory (androgen independent) metastatic prostate cancer treated; aged 18 years and older
Intervention(s)	75 mg/m^2 docetaxel + 40 mg plinabulin (IV) + 0.6 ml saline matching pegfilgrastim (subcutaneous)
Comparator(s)	75 mg/m^2 docetaxel + 250 ml D5W matching plinabulin (IV) + 0.6 ml pegfilgrastim (subcutaneous)
Outcome(s)	Primary outcome: Duration of severe neutropenia [Time frame: at the end of Cycle 1 (each cycle is 21 days)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**BPI-2358-106 Phase 2;** NCT04227990; Plinabulin vs. Pegfilgrastim in Reducing the Duration of Severe Neutropenia in Breast Cancer Patients Receiving Myelosuppressive Chemotherapy With Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) **Phase II – completed** **Location(s):** China and Ukraine **Study completion date:** January 2019
Trial design	Randomised, parallel assignment, open-label
Population	N=115 (actual); female adult patients who are candidates for adjuvant or neoadjuvant TAC with biopsy proven, early stage (Stage I and II) and Stage III breast cancer, and have not had prior chemotherapy; aged 18 years and older

Intervention(s)	For monotherapy, administered IV: • TAC and plinabulin 10 mg/m^2 OR • TAC and plinabulin 20 mg/m^2 OR • TAC and plinabulin 30 mg/m^2 For combination therapy, TAC, plinabulin (both IV) and pegfilgrastim (subcutaneous) were administered as follows: • TAC + 1.5 mg pegfilgrastim + 20 mg/m^2 plinabulin OR • TAC + 3 mg pegfilgrastim + 20 mg/m^2 plinabulin OR • TAC + 6 mg pegfilgrastim + 20 mg/m^2 plinabulin)
Comparator(s)	TAC (IV) and 6 mg pegfilgrastim (subcutaneous)
Outcome(s)	Primary outcome: Duration of severe neutropenia (DSN) [Time frame: Cycle 1 (21 days)]
Results (efficacy)	-
Results (safety)	-

Trial	**Protective-1; BPI-2358-105 Phase 2; NCT04345900;** A Phase 2, Multicenter, Randomized Study to Evaluate Duration of Severe Neutropenia With Plinabulin Versus Pegfilgrastim in Patients With Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy (Protective-1) **Phase II–** completed **Location(s):** USA, China, Russian Federation and Ukraine **Study completion date:** April 2018
Trial design	Randomised, parallel assignment, open-label
Population	N=55 (actual); adult patients with advanced or metastatic NSCLC failing platinum based therapy; aged 18 years and older
Intervention(s)	Interventions, administered IV, were as follows: • 75 mg/m^2 docetaxel + 20 mg/m^2 plinabulin OR • 75 mg/m^2 docetaxel + 10 mg/m^2 plinabulin OR • 75 mg/m^2 docetaxel + 5 mg/m^2 plinabulin
Comparator(s)	Docetaxel (75 mg/m2) and pegfilgrastim (6 mg)
Outcome(s)	Primary outcome(s): • Recommended Phase 3 Dose (RP3D) based on PK/PD analysis [Time frame: at the end of Cycle 4 (each cycle is 21 days)] • Duration of Grade 4 neutropenia (ANC < 0.5 × 109/L) [Time frame: at the end of Cycle 1 (each cycle is 21 days)] See trial record for full list of other outcomes
Results (efficacy)	Single dose-per-cycle plinabulin has a similar neutropenia protection benefit as pegfilgrastim. With each escalation of the plinabulin dose, the incidence of any grade of neutropenia decreased. There were no significant differences in mean (SD) days of severe neutropenia among those treated with pegfilgrastim (0.15 [0.38] days) when dosed at day 2 vs plinabulin 20 mg/m2 (0.36 [0.93] days; P=0.76) when dosed at day 1.[7]
Results (safety)	No safety signals were detected.[7]

ESTIMATED COST

The cost of plinabulin is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Neutropenic sepsis: prevention and management in people with cancer (CG151). September 2012.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

- Lucas AJ, Olin JL, Coleman MD. Management and Preventive Measures for Febrile Neutropenia. 2018.[25]
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- Smith TJ, Bohlke K, Armitage. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology clinical practice guideline update. 2015.[28]

ADDITIONAL INFORMATION

BeyondSpring Pharmaceuticals Inc. 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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