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HEALTH TECHNOLOGY BRIEFING
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JZP-458 for acute lymphoblastic leukaemia and lymphoblastic lymphoma

NIHRIO ID	28459	**NICE ID**	10488
Developer/Company	Jazz Pharmaceuticals UK Plc	**UKPS ID**	658977

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

SUMMARY

Acute lymphoblastic leukaemia (ALL) is a type of cancer affecting white blood cells, which results in overproduction of faulty cells. These cells take over the bone marrow leading to anaemia, infection, bruising and bleeding. ALL is a rare condition, usually affecting more children than adults. Lymphoblastic lymphoma (LBL) is similar to ALL, they differ in where they often occur in the body (lymph nodes and thymus gland in LBL, and blood and bone marrow in ALL), and they are both treated in the same way.

JZP-458 is an injection (which can be intramuscular or intravenous) that uses an enzyme called asparaginase, taken from a bacterium, to prevent cancer cells from growing and dividing. If licenced, JZP-458 would provide a treatment option for patients with ALL/LBL who are allergic to asparaginase taken from *E. coli* by using an alternative bacterium source.

PROPOSED INDICATION

JZP-458 is indicated for use as a component of a multi-agent chemotherapeutic regimen for the treatment of paediatric and adult patients, with acute lymphoblastic leukaemia (ALL)/lymphoblastic lymphoma (LBL), who have developed hypersensitivity or silent inactivation to *E. coli*-derived asparaginase.[a]

TECHNOLOGY

DESCRIPTION

JZP-458 (crisantaspase) is a recombinant *Erwinia chrysanthemi* L-asparaginase expressed in *Pseudomonas fluorescens*, with potential antineoplastic activity. JZP-458 hydrolyses L-asparagine to L-aspartic acid and ammonia. This depletes cancer cells of asparagine, which blocks protein synthesis and tumour cell proliferation.[1]

JZP-458 is in clinical development in a Phase II/III open-label, multicentre, dose confirmation, and pharmacokinetic study (NCT04145531) in patients (of any age) with ALL/LBL who are hypersensitive to *E. coli*-derived asparaginases (allergic reaction or silent inactivation). The study will determine the optimum dose and schedule of JZP-458 by both the intramuscular (IM) and intravenous (IV) administration.[2]

INNOVATION AND/OR ADVANTAGES

L-Asparaginase is an important component of ALL/LBL therapy. Hypersensitivity to *E. coli*-derived asparaginase therapy is associated with poor patient outcomes, and alternative options are required as a result. JZP-458 is a therapy that has no immunologic cross-reactivity to the currently used *E-coli*-derived asparaginases. As a result, it offers a treatment option for those who are hypersensitive to the currently existing asparaginase treatments, and who otherwise might not be able to receive their complete asparagine-depleting therapy.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

JZP-458 does not currently having Marketing Authorisation in the EU/UK for any indication.

[a] Information provided by Jazz Pharmaceuticals UK Ltd

PATIENT GROUP

DISEASE BACKGROUND

According to the World Health Organisation acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL) represent the same disease entity, which fall under B-cell and T-cell lymphoblastic leukaemias.[4] From a recent review of literature ALL/LBL comparisons have shown that they are likely to be different presentations of the same disease, however there is limited information about the genetic mutational differences of LBL compared to ALL.[5] Clinically, LBL is like ALL and the two conditions are treated in similar ways.[6,7] In LBL abnormal lymphocytes present in the lymph nodes or thymus gland, whereas in ALL the abnormal lymphocytes are mainly in the blood and bone marrow.[6]

ALL is a fast-growing type of blood cancer that starts from young white blood cells called lymphocytes in the bone marrow (the soft inner parts of the bones, where new blood cells are made). Normal lymphoblasts (immature white blood cells) can become either B lymphocytes (B-cells), T lymphocytes (T-cells) or natural killer cells, which all have roles in the immune system. In ALL there is uncontrolled growth of lymphoblasts. These immature cells are unable to fight infections as well as mature white blood cells, leaving the individual vulnerable to infection. They fill up the bone marrow, meaning there is not adequate space to make enough healthy white blood cells, red blood cells and platelets. This type of cancer usually develops quickly over days or weeks and is the most common type of leukaemia to affect children, but can also affect adults.[7-9]

It is not known what causes ALL, but exposure to certain risk factors can increase the likelihood of developing the disease. Risk factors include: radiation exposure, previous chemotherapy; presence of certain genetic disorders (including Down's syndrome, Fanconi anaemia and ataxia telangiectasia); various environmental factors (including smoking and being overweight or obese); and having a weakened immune system (as a result of HIV/AIDS or from taking immunosuppressants).[10,11]

The symptoms of ALL are vague and non-specific, resembling the symptoms of flu. The symptoms of ALL are caused when there are too many abnormal white blood cells, and too few normal red and white blood cells and platelets. Symptoms include general weakness, fatigue, fever, frequent infections, bruising or bleeding easily, weight loss, swollen lymph nodes, pain in the bones or joints, shortness of breath, feeling of fullness or discomfort in the abdomen and pale skin.[10,12]

CLINICAL NEED AND BURDEN OF DISEASE

ALL is a rare condition, with 803 new cases of ALL occurring in the UK between 2015-17. The incidence of ALL is strongly related to age, dropping sharply after childhood and reaching its lowest point at 30-34 years old in males (at an incidence rate of 0.6 per 100,000) and 35-39 years old in women (at an incidence rate of 0.2 per 100,000) in the UK in 2015. From this lowest point, incidence slightly increases reaching 11 per 100,000 in men and 12 per 100,000 in women at age 70-74 years in the UK in 2015. In the UK in 2013-2014, there were 175 new ALL cases reported in men aged over 20 years and 142 new ALL cases reported in women aged over 20 years.[13]

The five-year survival rate for ALL in England between 2008 and 2010 was 70%. However, this survival rate varied according to age:[14]

- Five-year survival rate of 90% for 14-year olds or younger
- Five-year survival rate of 70% for 15 – 24-year olds
- Five-year survival rate of 40% for 25 – 64-year olds
- Five-year survival rate of 15% for over 65-year olds

ALL accounts for less than 1% of all cancer deaths in the UK, with 232 deaths (equating to a mortality rate of 0.4 per 100,000) occurring due to ALL in England in 2017. Mortality is strongly related to age, with the highest mortality rates seen in older people. In the UK in 2015-17, on average each year 22% of deaths due to ALL were in people aged 75 years and older. The highest mortality rates in the UK in 2015-17 were seen in the 90+ age group for both men (mortality rate of 1.4 per 100,000) and women (mortality rate of 1.1 per 100,000).[15]

In England (2019-20) there were 32,182 finished consultant episodes (FCE) for ALL (ICD10 - C91.0) with 24,932 day cases and 47,517 FCE bed days. For LBL (ICD10 – C83.5) there were 2,012 FCE with 1,614 day cases and 2,763 FCE bed days.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of ALL/LBL is usually split into different phases, which include:[17-19]

- Induction stage (weeks to months) - the aim of this stage is to kill leukaemia cells in the bone marrow and restore the balance of healthy cells in the blood. It can comprise oral and intravenous chemotherapy, targeted therapies (imatinib and monoclonal antibodies), steroids, blood transfusions, antibiotics and pegaspargase.

- Consolidation stage (months) - the aim of this stage is to ensure any remaining cancer cells are killed by administering chemotherapy injections.

- Maintenance stage (two years) – the aim of this stage is to prevent the leukaemia returning by administering oral chemotherapy and monitoring (by regular check-ups). Treatment for relapsed and refractory ALL/LBL will include further chemotherapy (using different drugs from the initial treatment) or a stem cell transplant.[18]

CURRENT TREATMENT OPTIONS

Pharmacological treatment options for ALL/LBL include:[20]

- Pegaspargase – first-line, as part of antineoplastic combination therapy
- Erwinase – second-line as part of a chemotherapeutic regimen for patients who have developed hypersensitivity to *E. coli*-derived asparaginase[21]
- Blinatumomab – for treating ALL in remission with minimal residual disease activity
- Tisagenlecleucel, inotuzumab ozogamicin, blinatumomab, and ponatinib – for relapsed or refractory types of ALL

- Targeted therapies – imatinib and monoclonal antibodies

Current guidance advises treatment cessation if hypersensitivity occurs during treatment with pegaspargase.[22]

PLACE OF TECHNOLOGY

If licenced, JZP-458 would provide a treatment option for patients with ALL/LBL who have *E. coli* derived asparaginases hypersensitivity.

CLINICAL TRIAL INFORMATION

Trial	**NCT04145531; An Open-Label, Multicenter Study of Recombinant Crisantaspase Produced in *Pseudomonas Fluorescens* (RC-P) in Patients With Acute Lymphoblastic Leukemia (ALL)/Lymphoblastic Lymphoma (LBL) Following Hypersensitivity to *E. Coli*-derived Asparaginases** **Phase II/III:** Recruiting **Location(s):** USA and Canada **Primary completion date:** November 2021
Trial design	Open label, sequential assignment
Population	N=135 (planned); children and adults; diagnosis of ALL or LBL; previously had an allergic reaction to long-acting *E. coli*-derived asparaginase or have silent inactivation
Intervention(s)	• Part A – JZP-458 IM injection • Part B – JZP-458 IV injection
Comparator(s)	No comparator
Outcome(s)	• For Part A: Response Rate During the First Course of IM JZP-458 [Time Frame: 2 weeks] The response rate is defined as the proportion of patients with the last 72-hour NSAA level ⩾ 0.1 IU/mL during the first course of IM JZP-458 • Occurrence of treatment-emergent adverse events (TEAEs) [Time Frame: Up to 30 days after last dose] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of JZP-458 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. KTE-X19 for previously treated B-precursor acute lymphoblastic leukaemia (ID1494). Expected publication date: TBC
- NICE Technology appraisal guidance in development. KTE-C19 for previously treated B-precursor acute lymphoblastic leukaemia in people aged 2 to 21 (ID1336). Expected publication date: TBC
- NICE Technology appraisal guidance. Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity (TA589). July 2019
- NICE Technology appraisal guidance. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (TA554). December 2018
- NICE Technology appraisal guidance. Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (TA541). September 2018
- NICE Technology appraisal guidance. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451). June 2017
- NICE technology appraisal guidance. Pegaspargase for treating acute lymphoblastic leukaemia (TA408). September 2016
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). NHS England 16068/P. February 2017
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. NHS England B04/P/a. January 2015

OTHER GUIDANCE

- National Comprehensive Cancer Network. Acute Lymphoblastic Leukaemia. 2019.[23]
- European Society for Medical Oncology (EMSO). Acute Lymphoblastic Leukaemia: EMSO Clinical Practice Guidelines. 2016.[24]

ADDITIONAL INFORMATION

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