# Health Technology Briefing
# April 2024

# Human normal immunoglobulin for preventing primary infection in chronic lymphocytic leukaemia

| Company/Developer | Octapharma AG |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 30381 | NICE ID: Not available | UKPS ID: Not available |
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## Licensing and Market Availability Plans

Currently in phase III clinical trial.

## Summary

Human normal immunoglobulin (IVIG) is in development for preventing primary infection in patients with chronic lymphocytic leukaemia (CLL). CLL is the most common type of leukaemia, which is a cancer that affects blood cells in the bone marrow and progresses slowly over time. In CLL, the bone marrow makes too many unusual white blood cells called lymphocytes, which can build up in the bone marrow. This leaves less space for normal white blood cells, red blood cells and platelets to develop, which makes patients with CLL vulnerable to infection, especially when their levels of certain immunoglobulins (antibodies), such as IgG and IgA, are low. Infections are the cause of about 60% of deaths in CLL patients. Using immunoglobulin therapy to replace these antibodies can help cut down how often infections happen.

IVIG is a human immunoglobulin liquid preparation derived from healthy human plasma that contains immunoglobulin G (IgG). IgG are antibodies that help our body fight infections. IVIG contains a number of different antibodies, which prevent infection by attaching to the surface of invading organisms or agents that can produce disease, aiding in their removal before they can infect cells. If licensed, IVIG will offer an additional treatment option for the prophylaxis of primary infection in adult patients with CLL.

## Proposed Indication

Primary infection prophylaxis in adult patients with chronic lymphocytic leukaemia (CLL).[1]

# Technology

## Description

Human normal immunoglobulin (Panzyga; IVIG) is an intravenous human immune globulin, a 10% liquid preparation that contains immunoglobulin G (IgG).[2] IVIG is made from human plasma that is donated by healthy people and contains antibodies.[3] IVIG interacts with a number of different components of the immune system but its main mechanism of actions is believed to be Fc-dependent and F(ab')2-dependent. IVIG competitively blocks gamma Fc receptors, preventing the binding and ingestion of phagocytes and suppressing platelet depletion. IVIG contains several different antibodies, which prevent infection by attaching to the surface of invading pathogens and aiding in their disposal before they can infect cells. Antibodies remove pathogens via complement activation, agglutination or precipitation, pathogen receptor blocking, macrophage "tagging" or neutralisation (via binding) of pathogen toxins.[4]

IVIG is currently in clinical development for the prophylaxis of primary infection in CLL. In a phase III trial ("PRO-SID" Study, NCT04502030), patients will receive up to 13 infusions of IVIG in four-weekly intervals.[5]

## Key Innovation

CLL can cause secondary immunodeficiency, which results in a partial or full impairment of the immune system, leaving the patient unable to effectively resolve infections or disease.[5,6] Progressive CLL is associated with a reduction of IgG and IgA or hypogammaglobulinemia.[7] Therefore, patients are more susceptible to have recurrent infections when there is a deficiency of IG subtypes such as IgG3 and IgG4.[8] The use of immunoglobulin replacement therapy can be helpful in reducing the frequency of infection.[8] Adequate doses of IVIG may restore abnormally low IgG levels to the normal range in patients with CLL. [2] If licensed, IVIG will offer an additional treatment option for the prophylaxis of primary infection in adult patients with CLL.

## Regulatory & Development Status

IVIG currently has marketing authorisation in the UK for the following indications:[9]

Replacement therapy in adults, and children and adolescents (0 to 18 years) in:

- primary immunodeficiency syndromes with impaired antibody production; and
- secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of < 4 g/l.

Immunomodulation in adults, and children and adolescents (0 to 18 years) in:

- primary immune thrombocytopenia, in patients at high risk of bleeding or prior to surgery to correct the platelet count;
- Guillain Barré syndrome;
- Kawasaki disease (in conjunction with acetylsalicylic acid);
- chronic inflammatory demyelinating polyradiculoneuropathy; and
- multifocal motor neuropathy.

IVIG is in phase II/III clinical development for:[10]

- paediatric acute-onset neuropsychiatric syndrome;

- primary immune deficiency diseases; and
- autoimmune small fibre neuropathy.

## Patient Group

### Disease Area and Clinical Need

CLL is the most common type of leukaemia. It is a cancer of the white blood cells, in which the bone marrow makes too many abnormal white blood cells called lymphocytes. Over time, these abnormal lymphocytes build up in the lymphatic system and can build up in the bone marrow, leaving less space for normal white blood cells, red blood cells and platelets to develop.[11] Many people who have CLL do not have symptoms and symptoms are not always obvious at first; they can be similar to other conditions. The main symptoms of CLL include: swollen glands, usually in neck or under arms; weight loss; becoming ill a lot; feeling tired; a rash that looks like small bruises or bleeding under the skin and does not fade when a glass is rolled over it; bleeding or bruising for no reason; looking unusually pale and feeling breathless; a high temperature despite not being unwell; aches and pains that do not go away; and sweating at night.[12] Patients with CLL are predisposed to infections because of both the humoral immunodepression inherent to haematological disease, which is related to stage and duration of CLL, and to a further immunosuppression related to therapy.[13]

Up to 85% of CLL patients develop hypogammaglobulinemia (an immune system disorder) during the course of the disease.[7] The majority of patients with CLL will suffer from infections during their disease, accounting for approximately 60% of deaths in CLL.[14] CLL is rare in people under 40 and is more common in men.[12] Around 3800 people are diagnosed with CLL in the UK each year.[15] There are around 980 CLL deaths in the UK every year (2017 to 2019). Incidence rates for CLL in the UK are highest in people aged 85 to 89 (2016 to 2018), while mortality rates for CLL in the UK are highest in people aged 90 and over (2017 to 2019).[16] In England (2022-2023), there were 21,567 finished consultant episodes (FCE) and 20,624 admissions for CLL of B-cell type (ICD-10 code: C91.1), which resulted in 14,984 FCE bed days and 18,426 day cases.[17]

### Recommended Treatment Options

Currently, there is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) for the prophylaxis of infections in patients with CLL. The British Society for Haematology recommends the following prophylactic treatment options for patients with CLL:[18] pneumocystis *jirovecii* prophylaxis; immunoglobulin replacement therapy; vaccination against pneumococcal infections; and prophylactic antibiotics.

## Clinical Trial Information

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| Trial | **"PRO-SID" Study; NCT04502030; 2019-004375-40;** Double-blind, Randomized, Placebo-controlled, Prospective Phase III Study Evaluating Efficacy and Safety of Panzyga in Primary Infection Prophylaxis in Patients With Chronic Lymphocytic Leukemia<br>**Phase III** – recruiting<br>**Location(s):** Eight EU countries, USA, and other countries<br>**Primary completion date (estimated):** October 2024 |
| Trial Design | Randomised, parallel assignment, placebo-controlled, quadruple-blind |

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| Population | N = 240 (estimated); adults aged 18 and over with either treatment-naïve or relapsed/refractory CLL undergoing antineoplastic treatment |
| Intervention(s) | IVIG 10% (0.4 g/kg) plus standard of care prophylaxis[5] |
| Comparator(s) | Placebo plus standard of care prophylaxis[5] |
| Outcome(s) | Primary outcome measure: Occurrence of major infections [Time Frame: 52 weeks]<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of IVIG for prophylaxis of infection in adults with CLL is not yet known. The NHS indicative prices for normal immunoglobulin human (Panzyga) per vial are as follows:[19]

- 10g/100 ml solution for infusion £690
- 20g/200 ml solution for infusion £1380
- 5g/50 ml solution for infusion £345

## Relevant Guidance

### NICE Guidance

No relevant guidance identified.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig). 2021.

### Other Guidance

- Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. 2022.[18]
- Eichorst B, Robak T, Montserrat E, Chia P, Niemann CU, Kater AP, et al. Chronic Lymphocytic Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[20]

## Additional Information

Octapharma AG 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.

# References


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