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BPX-501 to improve immune recovery and Graft versus Host Disease (GvHD) after haploidentical stem cell transplant

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LAY SUMMARY

Haematopoietic stem cell transplantation (HSCT) is the treatment of choice with the intention of cure for some malignant and non-malignant blood disorders. HSCT involves a patient receiving stem cells (cells that can develop into different types of cells) to help the bone marrow produce healthy blood cells. For many patients who require HSCT, it is often difficult to find a fully matched donor. When the donor is partly matched to the patient (e.g. a close relative), the risk of the patient developing graft-versus-host disease (GvHD) is increased. In order to reduce the risk of GvHD, either the immune cells (T-cells) need to be removed or a post-transplant treatment is used to suppress the immune system.

BPX-501 is a medicinal product made of T-cells, a type of white blood cell, extracted from a donor who is partly matched to a patient undergoing HSCT. These T-cells are expected to help the patient to fight off viral infections while their immune system is being restored with the transplanted stem cells. However, the transplanted T-cells can cause GvHD. BPX-501 incorporates a safety mechanism where the T-cells are genetically modified to include a 'suicide gene'. If the patient develops GvHD, a medicine called rimiducid is given to switch on the suicide gene in the T-cells. This causes the T cells to die, thus preventing worsening of the GvHD. BPX-501 has the potential to reduce hospital admissions, infections and improve survival when used in combination with standard care.

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TARGET GROUP

Treatment of immunodeficiency and potential prevention of relapse in patients with malignant diseases; treatment of graft versus host disease (GvHD) following a haploidentical hematopoietic stem cell transplant (haplo-HSCT) in paediatric patients (1 month to 18 years old) with malignant and non-malignant diseases

TECHNOLOGY

DESCRIPTION

BPX-501 is an adjunct T-cell therapy administered after haploidentical haematopoietic stem cell transplant (haplo-HSCT), comprising genetically modified donor T-cells incorporating Bellicum's CaspaCIDe® safety switch (a mechanism for inducing cell death based on inducible caspase proteins to exploit the mitochondrial apoptotic pathway).[1] The CaspaCIDe system is designed to provide a safety net to eliminate alloreactive BPX-501 T-cells (via administration of activator agent rimiducid) should uncontrollable Graft versus Host Disease (GvHD) or other T-cell mediated transplant complications occur.[2]

BPX-501 is being developed to improve immune recovery and potentially decrease relapse of malignant disorders after mismatched, related, allogeneic transplantation in paediatric patients with malignant and non-malignant disorders amenable to HSCT.[3] The phase I/II trial (NCT02065869) includes the following subsets of patients (aged 1 month to 18 years):[4]

- patients with life-threatening acute leukaemia (high-risk Acute Lymphoblastic Leukaemia in 1st Complete Remission, Acute Lymphoblastic Leukaemia in 2nd CR, high-risk Acute Myelogenous Leukaemia in 1st Complete Remission, Acute Myelogenous Leukaemia in 2nd Complete Remission) or myelodysplastic syndromes;
- patients with non-malignant disorders deemed curable by allogeneic transplantation such as: primary immune deficiencies, severe aplastic anaemia not responding to immune suppressive therapy, osteopetrosis, selected cases of erythroid disorders such as β0 β0 thalassemia major, sickle cell disease, Diamond-Blackfan anemia;
- patients with congenital/hereditary cytopenia, including Fanconi Anaemia before any clonal malignant evolution (Myelodysplastic Syndrome, Acute Myelogenous Leukaemia).

In the currently ongoing phase I/II clinical trial, BPX-501 T cells are administered to all trial participants. The drug rimiducid is administered to participants who develop Grade III-IV acute GvHD, Grade II gut/liver acute GvDH or Grade I/II skin-only acute GvHD which is non-responsive after 7 days of standard of care treatment.[4]

BPX-501 does not currently have Marketing Authorisation in the EU for any indication. BPX-501 is also at phase II/III of development for blood cell cancer undergoing allogeneic (donor) blood stem cell transplant from a partially matched relative in adults.[5]

INNOVATION and/or ADVANTAGES

This medicinal product could be classed as an ATMP (advanced therapy medicinal product).[6] If licensed, BPX-501 will offer a treatment option for children between one month and 18 years of age with malignant and non-malignant diseases that have undergone an alpha/beta T-cell and CD19+ B cell depleted haplo-HSCT. Preliminary clinical trial results suggest that adding BPX-501 to a haplo-HSCT

has the potential to improve outcomes and to make the curative benefits of transplants available to more children with malignant and non-malignant diseases.[7]

The potential benefit of BPX-501 is multi-fold: the patient gets the benefit of having T-cells to fight infection, support engraftment, and prevent disease relapse and, should GvHD occur, the CaspaCIDe, a safety measure by which T-cells have been programmed with a self-destruct switch, can be triggered by the administration of rimiducid so that the T-cells can be destroyed if they start to react against tissues.[8] Other potential benefits may include faster hospital discharge and reduced costs of GvHD management.

DEVELOPER

Bellicum Pharmaceuticals

REGULATORY INFORMATION/ MARKETING PLANS

The European Medicines Agency (EMA) granted orphan drug designation to BPX-501 as an adjunct treatment following haematopoietic stem cell transplantation in June 2016.[9]

The EMA's Committee for Medicinal Products for Human Use (CHMP) has agreed that review and approval under "exceptional circumstances" may be suitable, recognizing that a randomized trial may not be feasible in the paediatric setting. In place of a randomized trial, the company intends to collect data from a concurrent observational study of allogeneic HSCT outcomes in the paediatric setting.[10]

The company anticipate submitting a Marketing Authorisation Application to the EMA (or MHRA) in 2019.[11]

PATIENT GROUP

BACKGROUND

A human leukocyte antigen (HLA) haploidentical donor is one who shares, by inheritance, precisely one HLA haplotype with the recipient and is mismatched for HLA genes on the unshared haplotype. HLA-haploidentical donors can be biological parents, biological children, full or half siblings, and collateral related donors. Allogeneic haematopoietic cell transplantation (HSCT) is the treatment of choice with the intention of cure for some malignant and non-malignant haematological disorders. The haematopoietic stem cells required for this procedure are usually obtained from the bone marrow or peripheral blood of a related or unrelated donor. Historically, the best results of allogeneic HSCT have been observed when the stem cell donor is a HLA-matched sibling, but, unfortunately, an HLA-matched sibling donor can be found in only approximately 30% of patients or less. For patients who lack an HLA-matched sibling, alternative sources of donor grafts can be found in suitably HLA-matched adult unrelated donors, unrelated umbilical cord blood donors, and partially HLA-mismatched-unrelated donors or HLA-haploidentical related donors.[12]

The major challenge of HLA-haploidentical HSCT is the intense bidirectional alloreactivity leading to high incidences of graft rejection and GvHD.[12]

According to the National Organization of Rare Diseases (NORD), GvHD is a rare disorder that can strike persons whose immune system is deficient or suppressed and who have received a bone

marrow transplant or a non-irradiated blood transfusion. Symptoms may include skin rash, intestinal problems and liver dysfunction.[13]

GvHD can be acute (sudden) or chronic (long lasting). Acute GvHD occurs in the first 100 days (at earliest 2 to 3 weeks) following bone marrow transplantation. The first symptoms are usually mild skin rash, liver dysfunction and intestinal problems. In some cases the patients may suddenly show very severe skin problems, diarrhoea, nausea, abdominal pain and liver failure. Chronic GvHD lasts beyond 100 days and usually persists long after a bone marrow transplant. The signs and symptoms are similar to those of acute GvHD, but in addition to the skin, intestinal and liver problems, chronic GvHD may also involve mucosa, lungs and the musculoskeletal system. Long term consequences may be scleroderma-like skin changes and bronchiolitis obliterans.[13]

GvHD affects males and females of all ages who have been immunosuppressed before being given a bone marrow transplant or a non-irradiated blood transfusion containing allogeneic lymphocytes. The risk of GvHD usually increases with the recipient's age and with the degree of HLA differences between donor and recipient unless fully T-cell depleted.[13] GvHD is a clinical diagnosis that may be supported with appropriate biopsies. The reason to pursue a tissue biopsy is to help differentiate from other diagnoses which may mimic GvHD, such as a viral infection (hepatitis, colitis) or drug reaction (causing skin rash). Acute GvHD is staged and graded (grade 0-IV) by the number and extent of organ involvement.[14] About 50% of patients with acute GvHD will eventually have manifestations of chronic GvHD. Patients with grade III/IV acute GvHD tend to have a poor outcome.[14]

Infection is an important cause of morbidity and mortality after HSCT. Engraftment after autologous HSCT occurs within 7–14 days and from 14 to 28 days after allogeneic HSCT. The risk of infection is related to the time period after transplantation, which can be defined as pre-engraftment, less than 3 weeks; immediate post-engraftment, 3 weeks to 3 months; and late post-engraftment, more than 3 months.[15]

CLINICAL NEED and BURDEN OF DISEASE

The number of allogeneic haematopoietic cell transplantations (HCTs) continues to increase, with more than 20,000 allogeneic transplantations performed annually worldwide. Allogeneic HCT from unrelated donors in the US surpassed the number from related donors after 2006 and the gap between these donor types continues to widen annually.[16]

In the EU, it is estimated that approximately 1 in 10,000 have haematopoietic stem cell transplants per year. This is equivalent to a total of around 51,000 people per year.[a] Using the 2016 mid-year population estimates for 0 to 18 year old for England and Wales, this would equate to 1,310 persons.[17]

About 35%-50% of HSCT recipients will develop acute GvHD. Given the number of transplants performed, it is estimated that about 5,500 patients per year will develop acute GvHD.[14] In the EU in 2016, it was estimated that graft-versus-host disease affected approximately 0.4 in 10,000 people. This was equivalent to a total of around 21,000 people,[b] applying the previous estimate for England

[a] The number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 513,700,000 (Eurostat 2016). Committee for Orphan Medicinal Products: EMA/COMP/388379/2016, July 2016.

[b] The number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 513,700,000 (Eurostat 2016). Committee for Orphan Medicinal Products: EMA/COMP/308001/2016, June 2016.

and Wales, the number of children that will develop GvHD after having undergone HCT would equate to 524.[17]

The incidence is directly related to the degree of human leukocyte antigens (HLA) disparity. For chronic GvHD, evidence from the US suggests that incidence ranges from 30% in recipients of fully histocompatible transplants to 60% to 70% in recipients of mismatched haematopoietic cells or haematopoietic cells from an unrelated donor. Factors that increase the incidence include use of peripheral blood rather than bone marrow as the source of haematopoietic cells and older recipient age. Factors predictive for poor survival following chronic GvHD diagnosis include a platelet count <100,000/mm^3 and history of acute liver GvHD.[16]

Transplantation mortality and morbidity rates have decreased considerably because of improved conditioning regimens, human leukocyte antigen (HLA) typing, supportive care, and prevention and treatment of serious infections. Overall and event-free survival rates depend on disease stage and pathology. Patients undergoing HLA-matched sibling allogeneic transplantation have the best 5-year survival rates.[15] Despite the early morbidity associated with HSCT, most of the transplant survivors attain high levels of physical and psychological quality of life (QoL). More than 90% of patients return to full-time employment within 3–5 years of transplantation. Disease-free patients have a 10-fold increased risk of mortality when compared with an age-matched general population at 2 years after allogeneic HSCT. Mortality remains high even 15 years after transplantation.[15]

In the UK, in the period April 2017 – Feb 2018 there were 223 adult donor provisions of stem cells.[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia (GID-TA10091). Expected publication date TBC.
- NICE technology appraisal in development. Tisagenlecleucel-T for previously treated B-cell acute lymphoblastic leukaemia in people aged 3 to 21 at initial diagnosis (GID-TA10270). Expected publication date TBC.
- NICE technology appraisal in development. LentiGlobin for treating beta-thalassaemia major (GID-TA10334). Expected publication date TBC.
- NICE technology appraisal. Pegaspargase for treating acute lymphoblastic leukaemia (TA408). September 2016.
- NICE technology appraisal. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399). July 2016.
- NICE technology appraisal. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.
- NICE technology appraisal. Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (TA322). September 2014.
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Sickle cell disease (QS58). April 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Haematopoietic stem cell transplantation (Children). B04/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for severe immunodeficiency and related disorders service (Children). B04/S(HSS)/b.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

None identified.

CURRENT TREATMENT OPTIONS

Treatment of GvHD usually consists of immunosuppressive drugs including glucocorticoid (steroid) drugs and a combination of cyclosporine (Sandimmune) and methotrexate. Instead of cyclosporine other calcineurin inhibitors (tacrolimus) or an mTOR inhibitor (sirolimus) may be chosen. In some cases, where GvHD is resistant to the above treatments antithymocyte globulin (ATG) may be used.

Prevention of GvHD consists of prophylactic treatment prior to bone marrow transplant, mostly using cyclosporine and T-cell depletion of the graft. Blood may be treated by radiation before being given to the recipient in order to suppress the donor's lymphocytes. These prophylactic measures often keep GvHD from developing.[13]

EFFICACY and SAFETY

Trial	NCT02065869, EudraCT 2014-000584-41**, PB-004; children aged 1 month to 18 years old; BPX-501 T cells and rimiducid; phase I/II**
Sponsor	Bellicum Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[4, 19]
Location	Italy, Spain, UK
Design	Non-randomized, single group assignment
Participants	n=193 (planned); aged 1 month to 18 years old; patients deemed clinically eligible for allogeneic stem cell transplantation that may have failed prior allograft; life-threatening acute leukaemia or non-malignant disorders deemed curable by allogeneic transplantation such as primary: a) immune deficiencies b) severe aplastic anaemia not responding to immune suppressive therapy c) osteopetrosis

	d) selected cases of erythroid disorders such as β0 β0 thalassemia major, sickle cell disease, Diamond-Blackfan anaemia.
Schedule	Experimental arm will receive TCR alpha beta depleted graft infusion with addback of BPX-501 T cells. Rimiducid dimerizer drug administered to subjects who develop Grade III-IV acute GvHD, Grade II gut/liver acute GvDH or Grade I/II skin-only acute GvHD which is non-responsive after 7 days of standard of care treatment.
Follow-up	Follow up for 180 days after transplant
Primary Outcomes	Event-Free Survival [Time Frame: 180 days after transplant]
Secondary Outcomes	• Treatment Related Mortality (non-malignant) or Non Relapse Mortality (malignant) [Time Frame: 100 days and 180 days after transplant] • Cumulative incidence and severity of acute (grade 2-4) and chronic GvHD at 180 days [Time Frame: 180 days after transplant] • Time to resolution of acute GvHD after administration of rimiducid [Time Frame: 180 days after transplant] • Immune reconstitution [Time Frame: 180 days after transplant]
Key Results	1. Data from an analysis of 98 patients with at least 180 days of follow-up were presented at the 22nd Congress of the European Haematology Association in Madrid, Spain. Key findings included: a. 59 non-malignant diagnoses, 39 malignant diagnoses b. Successful engraftment in 95% (93/98) patients c. 5% incidence transplant-related mortality (TRM) d. Rapid recovery of T-cells, B-cells, and immunoglobulins e. No post-transplant lymphoproliferative disorder (PTLD) f. 14% cumulative incidence of Grade 2–4 acute GvHD g. 3% cumulative incidence of chronic GvHD at 1 year for patients with ≥1 year of follow-up h. 11 patients who received rimiducid for acute or chronic GVHD had resolution of GVHD, with no recurrence 2. Data from a subset analysis of 38 children with paediatric acute myeloid leukaemia treated on the BP-004 study and a parallel U.S. BP-U-004 study were presented at the 23rd Congress of the European Haematology Association in Stockholm, Sweden. Key results included: a. 25 children were in CR2, 13 in CR1 b. Median follow-up was 470 days c. Relapse-free survival (RFS) for the overall cohort was 89.3% (95% CI, 79.3-99.2%). For CR1, the RFS was 83.9% (95% CI, 63.4-100%); for CR2, the RFS was 92.0% (95% CI, 81.4-100%) d. Overall survival (OS) for the overall cohort was 94.5% (95% CI, 87.1-100%). For CR1 OS was 83.9% (95% CI, 63.4-100%); for CR2 OS was 100%. e. The rates of grade I-IV, II-IV, and III-IV acute GVHD were 13.2%, 2.6%, and 0%, respectively. f. The cumulative incidence of chronic GVHD was 3%. g. 5 patients received rimiducid; the response rate was 80%. One patient without expansion of BPX-501 cells after infusion did not response to rimiducid. h. Immune recovery was rapid.

	3. Data from a subset analysis of 59 children with primary immunodeficiencies treated on the BP-004 study and a parallel U.S. BP-U-004 study were presented at the 23rd Congress of the European Haematology Association in Stockhold Sweden. Key results included: a. A wide variety of immunodeficiencies were treated. b. Median follow-up was 536 days. c. The graft failure rate was 5.1%. d. Transplant-related mortality was 8.7% e. Disease-free and overall survival were both 87.6% (95% CI, 79-96.3%) f. Grades II-IV and III-IV acute GVHD were 8.9% and 1.8%. g. Chronic GVHD occurred in 3% h. 7 patients received rimiducid for GVHD. Five of six evaluable patients responded to rimiducid. i. Immune recovery was rapid.
Adverse effects (AEs)	1. EHA 2017 preliminary analysis of 98 patients with at least 180 days of follow up showed 5% TRM. 2. EHA 2018 preliminary analysis of 38 patients with paediatric AML showed the following: 2 patients with > grade 1 non-GVHD treatment emergent AEs. AEs were grade 1-2. No grade 3-4 AEs or SAEs were reported. 3. EHA 2018 preliminary analysis of 59 patients with primary immunodeficiencies showed the following: 15.2% had > 1 AE reported. AEs were grade 1-2. X (tbc) number of SAEs were reported.
Expected reporting date	Study completion date reported as Dec 2019

ESTIMATED COST and IMPACT

COST

The cost of BPX-501 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Bellicum Pharmaceuticals

Bellicum Pharmaceuticals 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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