Innovation Observatory

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Human plasminogen for hypoplasminogenemia

NIHRIO ID	12754	**NICE ID**	9817
Developer/Company	Prometic Life Sciences Inc	**UKPS ID**	N/A

SUMMARY

Plasminogen (human) as intravenous infusion is in clinical development for people with hypoplasminogenemia. Hypoplasminogenemia is an ultra-rare, chronic, genetic condition associated with inflamed growths on the mucous membranes, the moist tissues that line body openings such as the eye, mouth, nasopharynx, trachea, and female genital tract. The growths are caused by the deposition of fibrin (a protein involved in blood clotting) and by inflammation. Growths can lead to severe medical problems including vision loss, ulcers of the gastrointestinal tract, and breathing difficulties caused by obstruction of the airway.

The medicinal product contains purified plasminogen extracted from human blood. Plasminogen is a naturally occurring protein that is primarily synthesized by the liver and circulates in the blood. Activated plasminogen, plasmin, is a fundamental component of the fibrinolytic system and is the main enzyme involved in the breaking down of blood clots and clearance of excess fibrin. Plasminogen is therefore vital in wound healing, cell migration, tissue remodelling, the formation of new blood vessels, and the development of embryos. When administered to patients who lack working plasminogen of their own, this plasma-derived protein replacement therapy is expected to replace the missing protein in their blood and correct the symptoms of the condition. If licensed, it may offer the first commercially available treatment option for patients with hypoplasminogenemia.

PROPOSED INDICATION

Hypoplasminogenemia (plasminogen deficiency type I)[1]

TECHNOLOGY

DESCRIPTION

Plasminogen (Ryplazim) contains purified plasminogen extracted from human blood.[2] Plasminogen (human) is a naturally occurring protein that is primarily synthesized by the liver and circulates in the blood. Activated plasminogen, plasmin, is a fundamental component of the fibrinolytic system and is the main enzyme involved in the lysis of blood clots and clearance of extravasated fibrin. Plasminogen is therefore vital in wound healing, cell migration, tissue remodelling, angiogenesis and embryogenesis.[3]

Plasminogen (human) is currently in clinical development for hypoplasminogenemia (plasminogen deficiency type I). In the phase II/III clinical trial (NCT02690714), plasminogen (human) is administered by intravenous (IV) infusion infusion at 6.6 mg/kg every 2 to 4 days with plasma samples taken before the 48 or 72 hours every 2 weeks for up to 12 weeks (Segment 2).[1]

INNOVATION AND/OR ADVANTAGES

Currently, there is no effective therapy commercially available for hypoplasminogenemia. [4] Plasminogen concentrates given locally and systemically have been shown to effectively prevent ligneous eye lesions from reforming after surgery.[5,6,7,8] When administered to patients who lack working plasminogen of their own, this novel, plasma-derived protein replacement therapy is expected to replace the missing protein in their blood and correct the symptoms of the condition. [2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Plasminogen (human) does not currently have Marketing Authorisation in the EU for any indication.[9]
Plasminogen is in phase Ib/II development for:[10]

- Plasminogen (human; sub-cutaneous) therapy in patients suffering from diabetic foot ulcers
- Plasminogen (human; sub-cutaneous) therapy in patients suffering from chronic tympanic membrane perforations

Plasminogen was granted EU orphan drug designation for plasminogen deficiency on 12 August 2015.[2]

PATIENT GROUP

DISEASE BACKGROUND

Inherited plasminogen deficiency can be divided into two types: true plasminogen deficiency (type I, or hypoplasminogenemia) and dysplasminogenemia (type II). Hypoplasminogenemia (congenital plasminogen deficiency or type I plasminogen deficiency) is caused by an alteration in the plasminogen gene which contains instructions for creating the protein plasminogen. Plasminogen is broken down by other enzymes into plasmin. Plasmin has several functions in the body. For example, plasmin breaks down another protein called fibrin. Fibrin is an important protein in the clotting of blood and wound healing. Due to the lack of plasminogen, fibrin abnormally accumulates in the body, causing inflammation and the ligneous growths that characterize hypoplasminogenemia.[11]

Hypoplasminogenemia is inherited in an autosomal recessive manner.[12] Autosomal recessive disorders are usually passed on by two carriers. Their health is rarely affected, but they have one mutated gene (recessive gene) and one normal gene (dominant gene) for the condition. With each pregnancy, two carriers have a 25% chance of having an unaffected child with two normal genes, a 50% chance of having an unaffected child who is also a carrier, and a 25% chance of having an affected child with two recessive genes.[13]

Hypoplasminogenemia is a rare multisystem disease associated with fibrinous deposition on mucous membranes throughout the body, primarily affecting the eyes, ears, sinuses, tracheobronchial tree, genitourinary tract, and gingiva.[14] Symptoms can occur in infants as early as 3 days of age but have also been reported for the first time much later in life, in adults as old as 61 years of age. Patients with hypoplasminogenemia may develop different types of woody-like lesions on mucous membranes in various parts of the body. These swollen lesions differ significantly by their size and the organ system that is involved in patients with these lesions and in the same patient over their lifetime, including:[15,16]

- **Eyes:** The most common symptom is called the ligneous conjunctivitis. This condition usually appears in infants and children. It is characterized by thick, yellow, white, or red lesions on the inside of the eyelids. In about one-third of the cases, these lesions form over the white outer layer of the eyeball. They may also grow onto the cornea, the clear layer that protects the iris and pupil. If left untreated, these lesions can tear the cornea, scarring, and can lead to vision loss or blindness.[7,16]

- **Gums:** The second most commonly affected site is the mouth. The lesions, while not painful, appear as bumps (ulcers) or a swelling of the gums. This condition can lead to the loss of teeth and the surrounding bone.[17]

- **Ears:** Lesions on the mucous membranes in the middle ear and eardrum may also develop. If left untreated, chronic ear infections and hearing loss could develop.[17]

- **Nose:** Ligneous lesions may also develop on the lining of the nose and sinuses.[18]

- **Respiratory tract:** When lesions develop in the windpipe, or air passage, they can lead to serious complications, such as pneumonia and a life-threatening airway obstruction, especially in children. These can also develop in the vocal cords and other areas in the respiratory tract.[17]

- **Gastrointestinal tract:** In some patients, lesions can be found on the mucous membranes that line the gastrointestinal tract, which often leads to ulcers.[17]

- **Kidneys:** Lesions can cause difficulty processing fluids and urinating because of the blockages they create.[17]

- **Female genital tract:** Lesions have been reported in girls as young as 2 years of age but are more frequently reported in adolescents and adult women. Painful menstrual cramps are the most common symptom in adult women.[15,19]

- **Skin:** A skin condition in children, called juvenile colloid millium, is also associated with hypoplasminogenemia. The lesions appear as small, yellow-brown, pimple-like swellings, typically located where the skin is exposed to the sun.[17]

- **Brain:** In a few rare cases, children who have hypoplasminogenemia are born with a build-up of fluid in the skull. This is known as congenital occlusive hydrocephalus. It occurs when the

fluid that surrounds and protects the brain and spinal cord (the cerebrospinal fluid) is blocked and unable to drain properly. The extra fluid in the baby's brain can cause brain damage, as well as mental and physical problems. Surgery is usually needed to help relive the obstruction. A deformity of the cerebellum, known as Dandy-Walker Syndrome, can also occur in children with hypoplasminogenemia. [16]

Genetic counselling may be of benefit for affected individuals and their families. Psychosocial support for the entire family is essential as well.[11]

CLINICAL NEED AND BURDEN OF DISEASE

The exact incidence or prevalence of the disorder is unknown, but one estimate places the incidence at 1.6 people per 1,000,000 in the general population.[11] As of 2015, plasminogen deficiency affected approximately 0.02 in 10,000 people in the European Union which was equivalent to a total of around 1,000 people.[2]

According to HES data for England, there were 82 finished consultant episodes (FCEs), 76 admissions and 69 FCE bed days due to other specified coagulation defects (ICD-10 D68.8).[20]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Diagnosis is based upon identification of characteristic symptoms, a family account of their medical history (anamnesis), a detailed patient history, and a thorough clinical evaluation. Specific laboratory tests can confirm a diagnosis specifically tests that measure the activity of plasminogen, which will be severely deficient in individuals with plasminogen deficiency type I. Antigen testing which measures the reactivity of plasminogen to a certain antigen may also be used. Molecular genetic testing can also detect alterations in the plasminogen gene known to cause the disorder.[11]

Although the characteristic lesions are now better recognized and plasminogen levels are accurately and easily measured, treatment options remain inadequate.[17] Symptomatic ligneous conjunctivitis has been managed case by case with varying levels of success.[5,6,7,8] Surgery has been the primary approach to treating ligneous conjunctivitis, but relief is temporary, and the lesions usually return. Steroidal treatment given intravenously has also had limited success in treating ligneous conjunctivitis. [7] Topical therapies have included hyaluronidase (an enzyme), heparin (a blood thinner or anticoagulant) used in combination with corticosteroids or alpha-chymotrypsin, and immunosuppressants (drugs that suppress the immune system), such as cyclosporine and azathioprine. However, therapies applied directly on lesions of the eye did not completely or consistently treat them or prevent them from reforming.[21,22,23,24]

Treatment may require the coordinated efforts of a team of specialists depending upon the specific organ system involved. For example, paediatricians, ophthalmologists, dental specialists, lung specialists (pulmonologists), and other health care professionals may need to systematically and comprehensively plan an affected child's treatment.[11]

CURRENT TREATMENT OPTIONS

The following treatment challenges are noted for congenital plasminogen deficiency:[11]

- There are no standardized treatment protocols or guidelines for affected individuals. Due to the rarity of the disease, there are no treatment trials that have been tested on a large group of patients.

- The only effective therapies reported in the medical literature are systemic and topical plasminogen concentrates that have led to an improvement in ligneous conjunctivitis and prevented recurrence in some patients following surgery. This includes eye drops that contain plasminogen, which have been effective in treating ligneous conjunctivitis. Plasminogen eye drops, however, are not readily available.
- Surgical removal of ligneous eye lesions may be beneficial initially, but the growths usually recur. Several medications have been tried including high-dose intravenous corticosteroid treatment, heparin, cyclosporine, azathioprine and hyaluronidase. There is a report of oral contraceptives leading to an increase of plasminogen level in one woman. These therapies have shown no or only limited benefit, or have only been reported in a single person.
- Some children with hydrocephalus may require surgical implantation of a shunt to drain away excess cerebrospinal fluid. Additional therapy is symptomatic and supportive.

PLACE OF TECHNOLOGY

If licensed, plasminogen may offer the first commercially available treatment option for patients with hypoplasminogenemia through the consistent increase of individual trough plasminogen activity levels.

CLINICAL TRIAL INFORMATION

Trial	NCT02690714; 2-80 years (inclusive); plasminogen (human) intravenous; phase II/III
Sponsor	Prometic Biotherapeutics, Inc
Status	Complete
Source of Information	Publication[25], trial registry[1], trial protocol[26], manufacturer[27]
Location	Norway & USA
Design	Single group assignment, open-label, repeat-dose study
Participants	n=15; aged 2-80 years (inclusive); documented history of lesions and symptoms consistent with a diagnosis of hypoplasminogenemia; plasminogen activity level ≤ 45%; documented vaccination to hepatitis A virus (HAV) and hepatitis B virus (HBV), or has received the first dose of HAV and HBV vaccine prior to the first dose of investigational drug and is scheduled to receive the second vaccine dose
Schedule	Plasminogen (human) was administered by IV infusion at 6.6 mg/kg every 2 to 4 days with plasma samples taken before the 48 or 72 hours every 2 weeks for up to 12 weeks (Segment 2). At the end of Segment 2, subjects had the option to participate in Segment 3 and attend site visits every 12 weeks for 36 additional weeks in Norway and until study termination by the sponsor for subjects in the USA.
Follow-up	Subjects in the USA were allowed to enrol in to an expanded access treatment protocol and continue to receive treatment with plasminogen (human) without any break in treatment.
Primary Outcomes	Number and percentage of patients who achieve target trough plasminogen activity levels, defined as an increase of individual plasminogen activity trough level by at least an absolute 10% above baseline for at least 3 measurements in 12 weeks. Primary end point success is defined as at least 80% of evaluable patient achieving target trough plasminogen activity levels.
Secondary Outcomes	Overall clinical success in the number and size of lesions or change in organ function at week 12 as compared with baseline assessments. Secondary end

	point success is defined as 50% of patients with clinically visible or other measurable lesions achieving ≥50% reduction in lesion number and/or size or improved organ function (e.g., improvement in forced expiratory volume in 1 second [FEV1]) from baseline. • Clinically visible lesions of the eyes and gingiva and manifestations of abnormal wound healing were imaged and analysed via digital photography, with each photograph including a millimetre scale to measure length and width. Clinically visible lesions that were too small to measure using the millimetre scale were described as non-measurable. Clinical Global Impression-Global Improvement (CGI-I) Scale (7-point scale) • A 7-item scale which captures the clinician's impression of the patient's disease improvement over time [Time Frame: Every 4 weeks for up to 12 weeks in Segment 2 and then at the 48 Weeks Visit in Segment 3] Quality of life scores • A short survey using a 10-point scale (0 = non-functioning, 10 = normal) using the American Chronic Pain Association Quality of Life Scale, with the investigator (or designee) asking questions to either the patient (≥12 years of age) or the parents of the patient (<12 years of age) documenting patient reported quality of life will be assessed at clinic visits [Time Frame: Every 4 weeks for up to 12 weeks and then at the 48 Weeks Visit] Safety • Safety included adverse events, clinical laboratory tests, anti-plasminogen antibodies, vital signs, and virology. The investigators collected adverse events in an unsolicited manner, which were graded by severity and assessed for causality. [Time Frame: Ongoing throughout the study]
Key Results	An interim analysis was performed after 10 patients completed 12 weeks of treatment (Segments 1 and 2); the interim data cut-off date of this analysis was 1 April 2017. The phase II/III trial met its primary and secondary endpoints following the intravenous administration of plasminogen to patients. Plasminogen treatment achieved a 100% success rate of its primary end point, namely, a targeted increase in the blood plasma concentration level of plasminogen as a surrogate target. Moreover, all patients who had active visible lesions when enrolled in the trial had complete healing of their lesions within weeks of treatment – a 100% patient response rate for this secondary end point. Preliminary data from the additional 36 week treatment period demonstrated that plasminogen treatment prevented the recurrence of lesions in the 10 patients treated with plasminogen for a total of 48 weeks.
Adverse effects (AEs)	Plasminogen was well tolerated in both adult and paediatric subjects and without any drug related serious adverse events.
Expected reporting date	Interim clinical study report issued on 5 March 2017. Final clinical study report expected to be issued Q2/2019.[a]

ESTIMATED COST

The cost of plasminogen is not yet known.

[a] Information provided by Prometic Life Sciences Inc

ADDITIONAL INFORMATION

Prometic Life Sciences 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.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- No relevant guidance identified.

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