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Taliglucerase alfa for Gaucher disease – first line

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Taliglucerase alfa for Gaucher disease – first line

Target group

- Type 1 Gaucher disease: adults with haematologic and/or skeletal involvement – first line.

Background

Gaucher disease is an inheritable, autosomal recessive disorder caused by insufficient activity of the enzyme glucocerebrosidase, responsible for metabolising lipids called glucocerebrosides. The accumulation of glucocerebroside in lysosomes of macrophages gives rise to Gaucher cells which occur throughout the liver, spleen, bone marrow, skeleton and occasionally the lung. This results in an enlarged liver and spleen (hepatosplenomegaly), anaemia and thrombocytopenia causing fatigue, discomfort, infections, bleeding and bruising, skeletal complications and other problems such as lung disease, impaired growth and delayed puberty[1,2].

Gaucher disease is commonly classified into three types, though in reality the wide range of gene mutations results in a variety of disease phenotypes. Type 1 is the most common form of Gaucher disease and is usually distinguished from types 2 and 3 by a variable age of onset and an absence of neurological symptoms, though a proportion of people with type 1 Gaucher do have neurological abnormalities[3]. Type 1 Gaucher varies in severity due to varying residual enzyme activity, ranging from mild asymptomatic cases (which may go undiagnosed) to severe, life threatening disease. Early onset in type 1 disease predicts a more aggressive course. Patients with the milder forms of type 1 may have a normal life expectancy, while untreated severe type 1 disease may lead to death from thrombocytopenic bleeding, asthenia or the complications of splenectomy within the first decade of life[4].

Technology description

Taliglucerase alfa is a plant cell expressed recombinant form of glucocerebrosidase produced in transformed carrot root cells. It is intended as a substitute enzyme replacement therapy (ERT) for the first line treatment of patients with Type 1 Gaucher disease. Taliglucerase alfa is administered by intravenous (IV) infusion at a starting dose range of 30U/kg to 60U/kg of body weight, given over 1 to 2 hours once every 2 weeks. Dosage may be adjusted depending on the individual patient.

Taliglucerase alfa is not in development for any other indications.

Innovation and/or advantages

Taliglucerase alfa is produced via an innovative plant cell expression system that does not require post-expression *in vitro* modification, does not use bovine serum albumin, and may offer improved safety from mammalian pathogens, oncogenic DNA, and endotoxins.

Developer

Protalix Biotherapeutics.

Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

Relevant guidance

- National Specialist Commissioning Advisory Group. UK national guideline for adult Gaucher disease. 2005[4].
- National Specialist Commissioning Advisory Group. Guidelines for the management of paediatric Gaucher disease in the UK[5].
- Haute Autorité de Santé. Gaucher disease: National diagnosis and treatment protocol. 2007[6].

Clinical need and burden of disease

Gaucher disease is a rare condition and the most prevalent of the lysosomal storage diseases. Over 90% of affected individuals have type 1 Gaucher disease[7] with high frequencies particularly seen in Ashkenazi Jews[4]. Prevalence of type 1 Gaucher disease has been estimated to be 1 in 200,000 (non-Ashkenazi Europeans)[4], equating to just over 300 people in the UK[a]. It is estimated that about 1 in 40,000 to 50,000 live births are affected by a form of Gaucher disease[2]. In 2008, 1,133 finished consultant episodes and 19 deaths were reported in England and Wales with the diagnosis of sphingolipodosis (ICD10 E75.2, includes Gaucher disease as well as other diseases).

Existing comparators and treatments

The UK National Guideline for Adult Gaucher Disease[4] recommends the following treatment options:

Enzyme replacement therapy (ERT):

- Imiglucerase (Cerezyme) – a modified form of human acid β-glucocerebrosidase produced through recombinant DNA technology using mammalian Chinese hamster ovary (CHO) cell culture. Treatment of choice for Type 1 and 3 Gaucher disease.
- Aglucerase (Ceredase) – no longer licensed for use. There is a limited residual supply for those patients unable to tolerate Cerezyme. The supply is unlikely to continue long term.

Substrate reduction therapy (SRT):

- Miglustat (Zavesca) – an oral daily therapy indicated for patients with mild to moderate Gaucher disease for whom ERT is not suitable.

Supportive therapy is indicated for all patients, and may include blood products, bisphosphonate therapy, and/or analgesia.

Patients identified with a Gaucher disease mutation, who may be asymptomatic and not require treatment, are monitored for disease progression at which time treatment options are reviewed.

Efficacy and safety

Trial	PB-06-001, NCT00376168; phase III.	PB-006-003, NCT00712348; phase III extension.	PB-06-002, NCT00712348; phase III.
Sponsor	Protalix Biotherapeutics.	Protalix Biotherapeutics.	Protalix Biotherapeutics.
Status	Complete and published in abstract.	Ongoing.	Ongoing.

[a] Based on UK population estimate from mid 2009.

Source of information	Trial registry[8] and manufacturer[9].	Trial registry[10] and manufacturer.	Trial registry[11] and manufacturer.
Location	USA, Canada, EU (inc UK), South Africa, Chile and Israel.	USA, Canada, EU (inc UK), Australia, South Africa, Chile and Israel.	USA, Canada, EU (inc UK), Australia and Israel.
Design	Randomised, dose comparison.	Non-randomised, uncontrolled, open label.	Non-randomised, uncontrolled, open label.
Participants and schedule	n=32; adults; Gaucher disease confirmed by enzymatic diagnosis; splenomegaly and thrombocytopenia; no neurological symptoms; not received ERT in last 12 mths. Randomised to taliglucerase alfa IV, either 30U/kg or 60U/kg, both given every 2 weeks for 38 weeks.	n=30; adults; completed trial NCT00376168. Taliglucerase alfa continued as assigned in study NCT00376168.	n=30; adults; Gaucher disease confirmed by enzymatic diagnosis; receiving imiglucerase ≥2 yrs; stable treatment regimen for ≥6 mths. Patients enter 12 week evaluation period to establish disease stability; then switched to taliglucerase alfa, dose equivalent to established imiglucerase dose, given IV every 2 weeks for 20 infusions.
Follow-up	Treatment period 38 weeks.	Treatment period 15 mths.	Treatment period 38 weeks.
Primary outcome	Spleen volume measured by MRI.	Spleen volume measured by MRI.	Adverse events.
Secondary outcomes	Liver volume, haemoglobin level, platelet count and biomarkers.	Liver volume, haemoglobin level, platelet count and biomarkers.	Spleen and liver volume, haemoglobin level, platelet count, biomarkers, pulmonary function test, ECG and anti human-prGCD antibodies.
Key results	For taliglucerase alfa dose 30U/kg and 60U/kg respectively (p-value, change from baseline): spleen volume reduction, 27% and 38% (both p<0.0001); liver volume reduction, 10% and 11% (both p<0.005); platelet count increased by 14% and 72% (both p<0.050); haemoglobin level increase 1.6g/dL and 2.2g/dL (both p<0.001); biomarker chitotriosidase levels decreased.	-	-
Expected reporting date	-	Feb 2011.	Dec 2010.
Adverse effects (AEs)	No serious AEs reported. Mild/moderate AEs reported 65 times in 30U/kg group and 72 times in 60U/kg group, including	-	-

	headache, hypersensitivity, dizziness, muscle spasm, skin irritation and arthalgia.		

Trial	PB-06-004, NCT00962260; expanded access.
Sponsor	Protalix Biotherapeutics.
Status	Ongoing.
Source of information	Trial registry[12] and manufacturer.
Location	USA and Israel.
Design	Non-randomised, open label.
Participants and schedule	n=200; adults; Gaucher disease requiring ERT; historically receiving imiglucerase but dose reduced or discontinued due to shortage of product. Taliglucerase alfa, dose equivalent to established imiglucerase therapy, given IV every 2 weeks
Follow-up	Treatment period 38 weeks.
Primary outcome	Adverse events.
Secondary outcomes	Clinical laboratory analysis, anti human-prGCD antibodies, biomarkers.
Expected reporting date	Trial due to complete once approval attained in relevant countries.

Estimated cost and cost impact

The cost of taliglucerase alfa is not yet known. Imiglucerase (Cerezyme) costs £1,071 per 400 unit vial. Between 15U/kg and 60U/kg are given every 2 weeks, equating to £3,089 to £12,357 for an average adult.

Claimed or potential impact – speculative

Patients

- ☐ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ None identified

Services

- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use
- ☐ Other:
- ☑ None identified

Costs

- ☐ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☐ New costs:
- ☐ Savings:
- ☑ Other: uncertain unit cost compared to current ERT

Other issues

- ☑ Clinical uncertainty or other research question identified: Pathophysiology of Gaucher disease not fully understood. Availability of new technologies may change treatment algorithms.
- ☐ None identified

References

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