Erythrocyte encapsulated asparaginase (GRASPA) for acute lymphoblastic leukaemia – second line

**SUMMARY**

Erythrocyte encapsulated asparaginase (GRASPA) is intended to be used in combination with chemotherapy for the treatment of acute lymphoblastic leukaemia (ALL) in adults and children who relapsed, or are intolerant to E. coli asparaginase. If licensed, it would offer an additional treatment option for these patients. Erythrocyte encapsulated asparaginase has the potential to improve safety through the use of erythrocytes as a biocompatible and biodegradable vehicle for L-asparaginase derived from *Escherichia coli*. Erythrocyte encapsulated asparaginase is an encapsulated L-asparaginase product, asparaginase hydrolyses asparagine to L-aspartic acid and ammonia, causing the depletion of asparagine, leading to the death of cells, such as leukaemic lymphocytes that require asparagine to survive.

ALL is the only form of leukaemia that is more common in childhood (under 15 years of age) and is characterised by a bimodal age pattern, with a peak incidence at one to four years of age and a second increase in incidence at ages over 60 years. In the case of childhood ALL, there is an overall survival rate of 80% at five years, but in adults the survival rate falls to 35% at five years. In England there were 529 new diagnoses of ALL registered in 2012. In the same year there were 202 deaths due to ALL registered in England.

Treatment of ALL consists of three phases: induction phase, consolidation phase and continuation treatment. CNS prophylaxis is also administered concurrently throughout treatment. The prognosis for patients with systemic relapse of ALL is poor. Treatment regimens for relapsed ALL are generally based on different combinations of the same agents used in frontline therapy in various doses and schedules. Erythrocyte encapsulated asparaginase is currently in one phase III clinical trial comparing its effect on efficacy and toxicity against treatment with native E.coli asparaginase. This trial was expected to complete in September 2014.
TARGET GROUP

• Acute lymphoblastic leukaemia (ALL): relapsed or intolerant to asparaginase derived from *Escherichia coli*; adults and children – second line.

TECHNOLOGY

DESCRIPTION

Erythrocyte encapsulated asparaginase (GRASPA; ERYASP; ERY-ASP) is an encapsulated L-asparaginase product for the treatment of recurrent acute lymphoblastic leukaemia (ALL) in adults and children. Asparaginase hydrolyses asparagine to L-aspartic acid and ammonia, causing the depletion of asparagine. This leads to the death of cells that require asparagine to survive, such as leukaemic lymphocytes. Therapeutic enzymes, like asparaginase, commonly cause significant toxicity, often have a short half-life, and eventually lead to the generation of anti-enzyme antibodies that decrease effectiveness. The new technology encapsulates asparaginase into red blood cells, so the enzyme is only active inside the erythrocyte. This increases the half-life of asparaginase and decreases the dose of enzyme required; one single injection may enhance the depletion of plasma asparagine for up to one month and reduce the occurrence and severity of adverse events. Anti-enzyme antibodies do not occur as the asparaginase is not extra-cellular. In the phase III clinical trial, erythrocyte encapsulated asparaginase is administered by intravenous injection (IV) at 150IU/kg once at each cycle of chemotherapy.

Erythrocyte encapsulated asparaginase does not currently have Marketing Authorisation in the EU for any indication. Erythrocyte encapsulated asparaginase is currently in phase II clinical trials for pancreatic cancer and acute myeloblastic leukaemia.

INNOVATION and/or ADVANTAGES

If licensed, erythrocyte encapsulated asparaginase will offer an additional treatment option for patients with ALL that have relapsed or are intolerant to *E. coli* asparaginase. Erythrocyte encapsulated asparaginase has the potential to improve safety through the use of erythrocytes as a biocompatible and biodegradable vehicle for L-asparaginase derived from *Escherichia coli*.

DEVELOPER

ERYtech Pharma; Orphan Europe (EU licence holder).

AVAILABILITY, LAUNCH OR MARKETING

Erythrocyte encapsulated asparaginase is a designated orphan drug in the EU and is currently in phase III clinical trials.
PATIENT GROUP

BACKGROUND

ALL is a malignancy of lymphocytes and lymphocyte-producing cells. In persons with ALL, there is excess production of immature lymphocyte-precursor cells, called blast cells, in the bone marrow. Eventually this overgrowth affects normal haemopoiesis, and there is a reduction in the numbers of red cells, white cells and platelets in the blood. The most common symptoms of ALL are:

- Anaemia, which results in fatigue and breathlessness.
- Low platelet counts, which may result in bruising and bleeding from mucous membranes and the gut.
- Low white cell counts, high numbers of abnormal cells and high metabolic rate, resulting in persistent infections and fever, which is often present even in the absence of clear indications of infection.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


CLINICAL NEED and BURDEN OF DISEASE

ALL is the only form of leukaemia that is more common in childhood (under 15 years of age) - it accounts for 75% of leukaemia diagnoses in paediatric patients. ALL is characterised by a bimodal age pattern, with a peak incidence at one to four years of age and a second increase in incidence at ages over 60 years. In the case of childhood ALL, there is an overall survival rate of 80% at five years, but in adults the survival rate falls to 35% at five years. In England there were 529 new diagnoses of ALL registered in 2012. In the same year there were 202 deaths due to ALL registered in England. In 2012, there were 25,330 hospital admissions for ALL (ICD10 C91.0) in England, resulting in 40,642 bed-days and 26,027 finished consultant episodes. The population likely to be eligible to receive erythrocyte encapsulated asparaginase could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

CURRENT TREATMENT OPTIONS

Treatment for ALL aims to induce clinical remission (induction phase), target cells that are clinically undetectable (consolidation phase) and maintain the patient in remission (continuation treatment). Additional CNS prophylaxis, which consists of concurrent chemotherapy, is also given throughout the entire period of treatment. Patients typically receive chemotherapy for 2.0-2.5 years. In adults, stem cell transplantation and chemotherapy are considered equal treatment options. Allogeneic haemopoietic stem cell transplantation is an option for children with very high risk or persistent disease, and high risk adults in remission.

The prognosis for patients with systemic relapse of ALL is poor. Treatment regimens for relapsed ALL are generally based on different combinations of the same agents used in frontline therapy in various doses and schedules. Treatment strategies mainly consist of risk-adapted, alternating short-course multiagent systemic and intrathecal chemotherapy, in some cases together with cranial/craniospinal irradiation, and conventional maintenance therapy. Tyrosine kinase inhibitor therapy with dasatinib may also be used to treat certain patients (Philadelphia-positive ALL patients with imatinib-resistant disease). Allogeneic stem cell transplant is also an option, where a suitably matched related or unrelated donor is found, although many patients with late relapse who respond well to re-induction chemotherapy can be cured without transplant. In the UK the vast majority of children and a smaller majority of adults with ALL are recruited to national and international trials, and managed according to the treatment schedules prescribed within the trials.

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>GRASPIVOTAL, GRASPELL2009-06, EudraCT2009-012584-34, NCT01518517; erythrocyte encapsulated asparaginase vs native E.coli asparaginase, both in combination with polychemotherapy; phase II/III.</th>
<th>GRASPELL2005-01, NCT00723346; erythrocyte encapsulated asparaginase vs native L asparaginase, both in combination with chemotherapy; phase II/II.</th>
<th>GRASPELL, GRAALLSA2-2008, NCT01523782: erythrocyte encapsulated asparaginase in combination with chemotherapy; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>ERYtech Pharma.</td>
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<td>ERYtech Pharma.</td>
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<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
<td>Published.</td>
<td>Complete but unpublished.</td>
</tr>
</tbody>
</table>

* Expert personal opinion.
<table>
<thead>
<tr>
<th>Source of information</th>
<th>Trial registry¹, manufacturer.</th>
<th>Publication², trial registry³, manufacturer.</th>
<th>Trial registry⁴, manufacturer.</th>
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<tbody>
<tr>
<td>Location</td>
<td>EU (not UK).</td>
<td>EU (not UK).</td>
<td>Not reported</td>
</tr>
<tr>
<td>Participants</td>
<td>n=80 (planned); aged 1-55 years; ALL; Philadelphia chromosome negative; 1ˢᵗ ALL relapse (isolated bone marrow relapse, combined medullary and extra-medullary relapse, or extra-medullary isolated CNS relapse), or lymphoblastic lymphoma (except Burkitt lymphoma), or failure of first line treatment (no complete remission obtained); previously treated with free or pegylated E. coli L-asparaginase; WHO performance status ≤ grade 2.</td>
<td>n=24; aged 1-55 years; ALL or lymphoblastic lymphoma (excluding Burkitt lymphoma); relapsed after first remission (medullary or CNS relapse), or refractory to first line chemotherapy; received E. coli l-ASNase during first line treatment; no cardiac, pulmonary, renal or hepatic disorders, no serious chronic infection or neurological dysfunctions (WHO grade &gt; 2), except for those related to leukaemia.</td>
<td>n=30; aged ≥ 55 years; ALL; newly diagnosed, treatment naïve; patient capable to receive polychemotherapy (WHO &lt;2); with or without meningeal disease; no ALL t(9;22) and/or not BCR-ABL positive; no severe infection, not HIV seropositive, and no active hepatitis related to B or C viral infection; no prior treatment with L-asparaginase (irrespective of the form); no history of grade 3 transfusional incident (life threatening); no presenting rare and/or dangerous anti-erythrocyte antibodies thus leading to unavailable phenotype compatible red blood cells.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to erythrocyte encapsulated asparaginase 150IU/kg IV injection once at each cycle of chemotherapy; or native E.coli asparaginase 10,000IU/m² IV 3-4 times (every 3 days) at each cycle of chemotherapy.</td>
<td>Randomised to erythrocyte encapsulated asparaginase 50IU/kg IV on day 4 or day 6 of induction therapy and day 6 of consolidation therapy⁵; 100IU/kg IV on day 4 or day 6 of induction therapy and day 6 of consolidation therapy; 150IU/kg IV on day 4 or day 6 of induction therapy and day 6 of consolidation therapy; or E. coli l-ASNase 10,000IU/m² IV every 3 days from day 4 or day 6 of each cycle.</td>
<td>Assigned to erythrocyte encapsulated asparaginase 50IU/kg IV on day 3 of induction phase 1 and day 6 of induction phase 2⁶; erythrocyte encapsulated asparaginase 100IU/kg IV on day 3 of induction phase 1 and day 6 of induction phase 2⁷ or erythrocyte encapsulated asparaginase 150IU/kg IV on day 3 of induction 1 phase and day 6 of induction 2 phase</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment for up to 10 cycles, follow-up 2 years.</td>
<td>Active treatment for 4 months, follow-up 8 months.</td>
<td>Active treatment for 2 months, follow-up 2 years.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Efficacy and toxicity combined (efficacy assessed according to mean duration of asparagine depletion and Duration of plasma asparagine depletion (&lt;2µmol/l).</td>
<td>Efficacy and toxicity combined (efficacy assessed according to percentage of patients with blood levels of plasma</td>
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</table>

⁵ Consolidation therapy was provided in erythrocyte encapsulated asparaginase arms if the patient fulfilled the following criteria: serum asparagine level >2µmol/l on day 1 of the consolidation phase, absence of any major complications (WHO grade >3) after the first administration, and no indication for haematopoietic stem cell transplantation.

⁶ A second injection, at the identical dose, will only be administered if no toxicity related to investigational product is observed and if the patient’s state of health allows it.
toxicity assessed according to incidence of allergic reactions of any grade).

### Secondary outcome/s

- Molecular response rate; plasma concentration of asparagine, aspartate, glutamine, glutamate and asparaginase, specific anti L-asparaginase antibodies; event free survival (EFS); relapse free survival; overall survival (OS); complete remission (CR).
- Pharmacokinetic and pharmacodynamic parameters, toxicity.
- Serum concentrations of asparagine, aspartate, glutamine, glutamate, asparaginase, and asparaginase; specific anti L-asparaginase antibodies; CR; cerebral spinal fluid concentrations of asparagine, aspartate, glutamine, and glutamate; OS; EFS; disease free survival.

### Key results

For the erythrocyte encapsulated asparaginase, native E.coli asparaginase, and HypSen<sup>d</sup> groups respectively:
- mean (SD) duration of asparaginase activity >100IU/l (days), 20.5 (±5.2), 9.4 (±7.4), 18.6 (±6.3); asparaginase related hypersensitivity, all grades, 0 (0%), 12 (43%), 3 (12%); asparaginase related hypersensitivity, grade ≥3, 0 (0%), 7 (25%), 0 (0%); CR, 17 (65%), 11 (39%), 14 (54%); minimal residual disease (MRD) <10<sup>-3</sup>, 9 (35%), 7 (25%), 6 (23%); 6 months OS, 92.3%, 78.6%, 73.1%; 12 months OS, 76.9%, 67.9%, 50.0%; 12 months EFS, 64.9%, 48.6%, 50.3%.

For the erythrocyte encapsulated asparaginase 50IU, 100IU,150IU, and E. coli l-ASNase groups respectively:
- mean (SD) duration (days) of asparagine depletion after the first injection, 8.63 (8.6), 9.03 (0.4), 18.57 (14.2), 20.65 (11.5).
- patients with blood levels of plasma asparagine ≤2µM ≥7 days, 0 (0%), 11 (51%), 10 (71%); patients with DLTs, 0 (0%), 2 (15%), 5 (36%); patients with blood levels of plasma asparagine ≤2µM ≥7 days and no DLTs, 0 (0%) 9, (69%), 7 (50%); CR, 33%, 77%, 64%.

For the erythrocyte encapsulated asparaginase 50IU, 100IU,150IU groups respectively:
- patients with blood levels of plasma asparagine ≤2µM ≥7 days, 0 (0%), 11 (51%), 10 (71%); patients with DLTs, 0 (0%), 2 (15%), 5 (36%); patients with blood levels of plasma asparagine ≤2µM ≥7 days and no DLTs, 0 (0%) 9, (69%), 7 (50%); CR, 33%, 77%, 64%.

### Adverse effects (AEs)

For the erythrocyte encapsulated asparaginase, native E.coli asparaginase, and HypSen<sup>d</sup> groups respectively:
- patients with at least 1 AE, 19 (73%), 28 (100%), 17 (65%); antithrombin III decrease, 4 (15%), 20 (71%), 6 (23%); hypofibrigenemia, 8 (31%).

Very common AEs (>10%)

- for the erythrocyte encapsulated asparaginase and E. coli l-ASNase groups respectively:
- allergic reaction grade III and IV, 0%, 33%; pancreatic enzymes elevation, 16%, 17%; hepatic disorder, 38%, 50%; hypoalbuminaemia/Very common AEs (>10%): DLTs, 7 (23%), grades 3-4 infection, 21 (70%), invasive fungal infection, 9 (30%), grade 3-4 pancreatic enzyme elevation, 11 (37%), grade 3-4 liver enzyme elevation, 20 (66%), hypoalbuminemia, 13 (43%), antithrombin (AT-

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<sup>d</sup> Patients with prior hypersensitivities to asparaginase who could not be randomised to native asparaginase were placed in the exploratory 'HypSen' arm, and treated with erythrocyte encapsulated asparaginase.
NIHR Horizon Scanning Centre

| Expected reporting date | 19 (68%), 7 (27%). | proteinaemia, 0%, 33%; coagulation disorder, 16%, 66%. | III) < 60% (or AT-III substitution), 21 (70%). |

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**ESTIMATED COST and IMPACT**

**COST**

The cost of erythrocyte encapsulated asparaginase is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Other: the drug is designed to reduce morbidity due to asparaginase hypersensitivity reactions. It may also carry a reduced risk of other side effects such as thrombosis but that has yet to be proven*.
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Re-organisation of existing services
- Other: A blood sample from the patient has to be sent to the company to formulate the encapsulated asparaginase. The logistics of this could be challenging depending on volume, transport and regulatory requirements that apply to transfusion of blood products*
- Decreased use of existing services
- Need for new services
- None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Other increase in costs
- Other: uncertain unit cost compared to existing treatments
- Reduced drug treatment costs
- Other reduction in costs
- None identified

**Other Issues**

- Clinical uncertainty or other research question identified
- None identified

* Expert personal opinion.
REFERENCES


21 Clinicaltrials.gov. Administration of allogenic red blood cells loaded L-asparaginase in cases of relapse of acute lymphoblastic leukaemia (GRASPALL).  

22 Clinicaltrials.gov. Administration of GRASPA (suspension of erythrocytes encapsulating L-asparaginase) in elderly patients with first line acute lymphoblastic leukemia.  