Epratuzumab for systemic lupus erythematosus

**SUMMARY**

Epratuzumab is intended to be used as a first line therapy for the treatment of active, moderate to severe systemic lupus erythematosus (SLE). If licensed, it will offer an additional treatment option for these patients, a group who currently have few effective therapies available. Epratuzumab is a humanised antibody targeting the CD22 receptor, a transmembrane sialoglycoprotein expressed on mature B-cell lineages that influences migration and activation. The mechanism of action of epratuzumab is not yet fully defined, but it may selectively modify B-cell activation and function. Epratuzumab does not currently have a Marketing Authorisation in the EU for any indication.

There are currently around 15,000 people in England and Wales with SLE and approximately 2,000 people are diagnosed with SLE each year. Annual incidence is estimated to be from 2.0 to 7.6 cases per 100,000 of the population. Although the severity of the disease is typically greater in males, SLE affects women more often than men. SLE mainly affects people aged 15-60 years. An estimated 40–70% of patients with SLE develop renal involvement, and neuropsychiatric involvement occurs in 27% of people with SLE. Approximately 20-30% of patients with SLE continue to have high disease activity despite standard therapies or have organ involvement particularly associated with a worse prognosis. There were 164 deaths due to SLE registered in England and Wales during 2012.

Current treatment strategies for SLE depend on the severity of disease and organ involvement. Treatment options include antimalarials, non-steroidal anti-inflammatory drugs (either alone or in combination with glucocorticoids), immunosuppressive agents, biological disease-modifying anti-rheumatic drugs (DMARDS), and non-biological DMARDS. Epratuzumab is currently in three phase III clinical trials comparing its effect on combined response criteria against treatment with placebo. These trials are expected to complete in May 2015 and January 2019.
TARGET GROUP

- Systemic lupus erythematosus (SLE): moderate to severe; active – in addition to standard of care.

TECHNOLOGY

DESCRIPTION

Epratuzumab (AMG-412; IMMU-103; IMMU-LL2) is a humanised antibody targeting the CD22 receptor, a transmembrane sialoglycoprotein expressed on mature B-cell lineages that influences migration and activation. The mechanism of action of epratuzumab is not yet fully defined, but data indicates that it selectively modifies B-cell activation and function. In the phase III clinical trial, it is administered by intravenous (IV) infusion at 600mg weekly for 4 consecutive weeks of a 12-week treatment cycle, or 1,200mg every other week for 4 consecutive weeks of a 12-week treatment cycle.

Epratuzumab does not currently have a Marketing Authorisation in the EU for any indication. Epratuzumab is currently in phase III clinical trials for acute lymphoblastic leukaemia (combination therapy), and phase II clinical trials as combination therapy for diffuse large B-cell lymphoma and non-Hodgkin's lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, epratuzumab will offer an additional treatment option for adults with active, moderate to severe SLE, a group who currently have few effective therapies available.

DEVELOPER

Immunomedics; UCB (EU licensee).

AVAILABILITY, LAUNCH OR MARKETING

Epratuzumab is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic relapsing and remitting multi system autoimmune disease characterised by inflammation and organ damage. SLE affects the whole body including the skin, joints, internal organs and serous membranes, and results in chronic debilitating ill health. It is a life-long and potentially life-threatening condition for which there is no cure. The cause of SLE is not yet completely understood, although genetic, hormonal and environmental factors are thought to play a role in the development and progression of the disease. Known epidemiological risk factors for SLE include smoking, ultraviolet radiation and certain medications. Disease activity varies over time and, at the onset, symptoms may include unexplained fever, extreme fatigue, muscle and joint pain, and skin rash. The disease course may be variable and is characterised by periods of disease remission punctuated by flares of disease activity that can be prolonged and
SLE is associated with considerable morbidity and mortality, with 10-year survival rates ranging from 70% to 92%. The main risk factor for mortality in SLE is organ damage, which in turn is driven by disease activity. SLE may lead to complications such as arthritis, kidney failure, heart and lung inflammation, central nervous abnormalities and blood disorders. Long-term damage accrues as a result of persistent disease activity and the cumulative effects of glucocorticoids.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

There are currently around 15,000 people in England and Wales with SLE and approximately 2,000 people are diagnosed with SLE each year. In the United Kingdom, prevalence is estimated to be from 12.5 to 207 cases per 100,000 depending on study period and population studied, and annual incidence is estimated to be from 2.0 to 7.6 cases per 100,000 population. The prevalence of SLE is significantly higher in African-Caribbean, South Asian and Chinese populations compared with European white populations. Although the severity of the disease is greater in males, SLE affects women more often than men; women account for 90% of SLE patients. SLE mainly affects people aged 15-60 years old, and the majority of diagnoses are in women aged 15 to 45 years. However, in those diagnosed after the age of 50 years, the proportion of new cases who are women falls to 75%.

An estimated 40–70% of patients with SLE develop renal involvement, and approximately 10% of patients with lupus nephritis develop end-stage renal failure requiring dialysis or transplantation. Neuropsychiatric involvement occurs in 27% of people with SLE and has a wide variety of clinical presentations, including seizures, chronic headache, transverse myelitis, vascular brain disease, psychosis, and neural cognitive dysfunction. SLE is also characterised by haematological features, such as haemolytic anaemia (8%), thrombocytopenia (22%) and lymphadenopathy (12%), and cardiovascular complications, such as thrombosis (14%) and Raynaud’s phenomenon (34%). Approximately 20-30% of patients with SLE continue to have high disease activity despite standard therapies or have organ involvement particularly associated with a worse prognosis, e.g. renal, neuropsychiatric or haematological involvement. In 2012-13 there were 4,038 admissions for SLE (ICD-10 M32) in England, resulting in 9,595 bed days and 4,574 finished consultant episodes. There were 164 deaths due to SLE (ICD-10 code M32) registered in England and Wales during 2012.

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* Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Systemic lupus erythematosus (autoantibody-positive) - belimumab (ID416). Expected date of issue to be confirmed.

Other Guidance

- Arthritis Research UK. Overview of the management of systemic lupus erythematosus. 201311.
- Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. 201212.
- American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. 201212.
- EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. 201014.

CURRENT TREATMENT OPTIONS

The aims of current treatments for SLE are: managing acute periods of potentially life-threatening ill health, minimising the risk of flares during periods of relative stability, and controlling the less life-threatening, but often incapacitating day-to-day symptoms17. Treatment strategies depend on the severity of disease and organ involvement.

Antimalarials (especially hydroxychloroquine) and non-steroidal anti-inflammatory drugs, either alone or in combination with glucocorticoids, are standard therapy for those with mild to moderate skin and joint disease7,8. In non-responsive patients or patients not able to reduce glucocorticoids below doses acceptable for chronic use, immunosuppressive agents such as azathioprine and methotrexate should also be considered for moderate skin and joint disease12. Those refractory to this treatment require more potent immunosuppression therapy, such as IV cyclophosphamide or mycophenolate mofetil7. Biological disease-modifying anti-rheumatic drugs (DMARDS) are used in patients with severe disease who do not respond to conventional treatments or require unacceptably high doses of glucocorticoids7,12,17. Treatment options for SLE may include7,18,19:

b Expert personal communication.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Antimalarial drugs – hydroxychloroquine sulphate.
- Glucocorticoids:
  - Topical and low-dose oral: for mild SLE.
  - Oral, intramuscular or intra-articular: for moderate SLE.
  - Intravenous high-dose: for serious, life- or organ-threatening SLE.
- Immunosuppressive/cytotoxic agents:
  - Non-biological DMARDS (unlicensed for this indication) – azathioprine, methotrexate, mycophenolate mofetil, ciclosporin, tacrolimus, cyclophosphamide.
  - Biological DMARDS – belimumab, rituximab (unlicensed for this indication).

Additional treatment options that are considered for severe SLE with or without renal involvement may include:
- Plasmapheresis: for antiphospholipid syndrome, thrombotic thrombocytopenic purpura and pulmonary haemorrhage
- Immunoglobulin IV
- Dapsone (unlicensed for this indication): for cutaneous lupus not responding to antimalarials
- Gonadotrophin inhibitor – danazol (unlicensed for this indication): to protect against cyclophosphamide induced ovarian toxicity

SLE patients who develop chronic kidney disease or end-stage renal failure may receive dialysis and renal transplantation as indicated for end-stage renal failure from any cause.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01408576; epratuzumab 600mg vs epratuzumab 1,200mg; phase III extension.</td>
<td>UCB Pharma.</td>
<td>Ongoing.</td>
<td>Trial registry, manufacturer.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Randomised, active-controlled.</td>
<td>n=1,400 (planned); aged ≥18 years; completed study NCT01262365 or NCT01261793, or terminated these studies prematurely at week 16 or later due to lack of efficacy and would, in the opinion of the investigator, continue to benefit from continued epratuzumab.</td>
</tr>
<tr>
<td>NCT01262365; epratuzumab vs placebo; phase III.</td>
<td>UCB Pharma.</td>
<td>Ongoing.</td>
<td>Trial registry, manufacturer.</td>
<td>EU (incl UK), USA, and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=780 (planned); aged ≥18 years; positive antinuclear antibodies (ANA); clinical diagnosis of SLE by American College of Rheumatology (ACR) (at least 4 criteria met); active moderate to severe SLE activity as demonstrated by BILAG. and SLEDAI total scores; on stable SLE treatment regimen, including mandatory corticosteroids</td>
</tr>
<tr>
<td>NCT01261793; epratuzumab vs placebo; phase III.</td>
<td>UCB Pharma.</td>
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<td>EU (incl UK), USA, Canada and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=780 (planned); aged ≥18 years; ANA positive; clinical diagnosis of SLE by ACR (at least 4 criteria met); active moderate to severe SLE activity as demonstrated by BILAG and SLEDAI total scores; on stable SLE treatment regimen, including mandatory corticosteroids</td>
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© British Isles Lupus Activity Group (BILAG)

*d* Systemic Lupus Erythematosus Activity Index (SLEDAI)
<table>
<thead>
<tr>
<th>Schedule</th>
<th>Randomised to, epratuzumab 600mg IV infusion weekly for 4 consecutive weeks of a 12-week treatment cycle; or epratuzumab 1,200mg IV infusion every other week for 4 consecutive weeks of a 12-week treatment cycle.</th>
<th>Randomised to, epratuzumab 600mg IV infusion weekly for 4 consecutive weeks of a 12-week treatment cycle; or epratuzumab 1,200mg IV infusion every 2 weeks, with placebo IV infusion every 2 weeks, for 4 consecutive weeks of a 12-week treatment cycle; or placebo IV infusion weekly for 4 consecutive weeks of a 12-week treatment cycle.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Active treatment for up to 16 cycles (192 weeks), follow-up 4 weeks, or 13 weeks after the final dose of study drug for subjects who discontinue early.</td>
<td>Active treatment for 48 weeks, follow-up for 4 weeks (for subjects not entering the open-label extension study NCT01408576), or 13 weeks after final dose of study drug for subjects who discontinue early.</td>
<td>Active treatment for 48 weeks, follow-up for 4 weeks (for subjects not entering the open-label extension study NCT01408576), or 13 weeks after final dose of study drug for subjects who discontinue early.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Number of subjects prematurely discontinuing due to a treatment-emergent adverse event (TEAE) during the treatment period; number of subjects reporting at</td>
<td>Subjects meeting novel composite endpoint — BICLA (British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment) at week 48.</td>
<td>Subjects meeting treatment response criteria (BICLA) at week 48.</td>
</tr>
</tbody>
</table>
least 1 serious adverse event (SAE) during the treatment period.

### Secondary outcome/s

**Response to treatment**

- **Treatment response criteria:**
  - British Isles Lupus Activity Group (BILAG) improvement,
  - no worsening in Systemic Lupus Erythematosus Activity Index (SLEDAI),
  - no worsening in Physician's Global Assessment of Disease (PGA),
  - no disallowed changes in concomitant medications (including increase in corticosteroids, immunosuppressants, and antimalarials)

- **Quality of life (QoL) assessed by:**
  - SF-S6,
  - EQ-5D,
  - LupusQoL

- **Fatigue assessed by:**
  - FACIT-fatigue

**Subjects meeting treatment response criteria at week 12**

**Subjects meeting treatment response criteria at week 24**

**Subjects meeting treatment response criteria at week 36**

**Change in daily corticosteroid dose at week 24**

**Change in daily corticosteroid dose at week 48**

**QoL assessed by:**

- SF-S6,
- EQ-5D,
- LupusQoL

**Fatigue assessed by:**

- FACIT-fatigue

### Study completion date

- **NCT00383513:**
  - Epratuzumab; phase II extension
  - Study completion date reported as May 2015.

- **NCT00660881:**
  - Epratuzumab; phase II
  - Study completion date reported as May 2015.

- **NCT00624351:**
  - Epratuzumab vs placebo; phase II
  - Study completion date reported as May 2015.

### Source of information

- **T**rial registry
- **P**ublication
- **M**anufacturer

### Design

- **Uncontrolled, single arm**

### Participants

- **n=29; aged ≥18 years:**
  - participated in study NCT00111306 or NCT00383214, and believed to have benefitted from participation in those studies;
  - no toxicity to epratuzumab;
  - no significant protocol deviations during the NCT00111306 or NCT00383214 studies;
  - no evidence of significant

- **n=203; aged ≥18 years:**
  - patients from NCT00624351 who completed through week 12 of the study or who terminated early at week 8 or later due to treatment failure;
  - patients must have maintained eligibility requirements throughout their study participation;
  - no active severe SLE disease activity which

- **n=227; aged ≥18 years:**
  - diagnosis of SLE by ACR revised criteria (at least 4 of the 11 criteria met);
  - ANA positive; active moderate or severe SLE disease activity as demonstrated by BILAG A level disease activity in at least one body/organ system or BILAG B level disease activity in at least two body/organ systems; if

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* NCT00111306 (ALLEVIATE-1; SL0003) and NCT00383214 (ALLEVIATE-2; SL0004) were phase III clinical trials of epratuzumab initiated in patients with BILAG A and BILAG B SLE activity, respectively, which terminated early due to interruption of drug supply.
### Infection

Involves the renal system or the CNS system, including transverse myelitis, psychosis and seizures; no history of anti-phospholipid antibody syndrome and use of oral anticoagulants or anti-platelet treatment; no history of chronic infection, recent significant infection, or any current sign of symptom that may indicate infection.

### On Antimalarials

Dose regimen must be stable for 4 weeks; no active severe SLE disease activity which involves the renal system or CNS including transverse myelitis, psychosis, and seizures; no history of anti-phospholipid antibody syndrome and use of oral anticoagulants or anti-platelet treatment; no history of chronic infection, recent significant infection, or any current sign of symptoms that may indicate infection.

### Schedule

| Epratuzumab 360mg/m² IV infusion on week 0 and week 1 of a 12 week maintenance cycle. | Epratuzumab 1,200mg IV infusion on week 0 and week 2 of a 12 week treatment cycle. | Randomised to, epratuzumab 100mg IV infusion on weeks 0, and 2, and placebo on weeks 1 and 3; epratuzumab 400mg IV infusion on weeks 0, and 2, and placebo on weeks 1 and 3; epratuzumab 600mg IV infusion on weeks 0, 1, 2, and 3; epratuzumab 1,200mg IV infusion on weeks 0, and 2, and placebo on weeks 1 and 3; epratuzumab 1,800mg IV infusion on weeks 0, and 2, and placebo on weeks 1 and 3; or placebo IV infusion on weeks 0, 1, 2, and 3. |

### Follow-up

| Active treatment for 4 cycles (48 weeks), follow-up 6 years. | Study was closed early due to logistical considerations; median (range) duration of epratuzumab exposure was 845 (75–1,185) days (2.3 years). Follow-up 12 weeks after final dose of study drug for subjects not entering NCT01408576. | Active treatment for 12 weeks, follow-up 12 weeks after final dose of study drug for subjects not entering NCT00660881. |

### Primary outcome/s

| Number of subjects reporting ≥1 SAE; discontinuation of treatment due to TEAEs. | AEs. | Response at week 12 according to a combined response index (BICLA). |

### Secondary outcome/s

| Time to treatment failure; pharmacokinetics; anti-epratuzumab antibodies; change from baseline in short form 36-items health survey (SF-36) physical component summary | Combined response index analysis evaluating BILAG, SLEDAI, PGA, and treatment failure status; combined response index including SF-36 response; BILAG score; SLEDAI | BICLA response at weeks 4 and 8; response at week 4, 8, and 12 according to a combined response index including SF-36 response; BILAG scores at week 4, 8, 12, and 24; SLEDAI |
(PCS) score and mental composite summary (MCS) score; patient's global assessment of disease activity (PtGADA); physician's global assessment of disease activity (PGADA).

scores; patient and physician visual analogue scale (VAS); SF-36 stabilisation or improvement; SF-36 PCS and MCS scores; EQ-5D; treatment failure; total daily steroid dose; time to flare for patients who entered the study without flare as defined by BILAG; time to sustained response for patients entering with flare as defined by BILAG; immunogenicity as measured by human anti-human antibodies (HAHA); changes in levels of circulating B and T cells.

scores at week 2, 4, 8, and 12; PGA scores at week 12; SF-36 response at week 2, 4, 8, and 12; EQ-5D score at week 12; treatment failure up to week 12; cumulative steroid dose at week 12; HAHA levels at week 12; levels of circulating B-cells at week 12.

### Key results

35% of participants reported ≥1 SAE; 10% of participants discontinued treatment due to a TEAE.

Patients with combined response (BILAG improvement without worsening, no SLEDAI worsening, no PGA worsening, relative to NCT00624351 baseline) at screening, week 24, 48, 72, 96, and 108, respectively: 32.5%, 40.7%, 48.4%, 57.2%, 56.5%, 60.3%.

For the epratuzumab 100mg every other week (EOW), 400mg EOW, 600mg weekly, 1,200mg EOW, 1,800mg EOW, and placebo weekly groups, respectively: BICLA responders, 30.8%, 26.3%, 45.9%, 40.5%, 23.7%, 21.1%.

### Adverse effects (AEs)

**Very common AEs (>10%):**
- conjunctivitis, 10%; upper respiratory tract infection, 45%; urinary tract infection, 28%; diarrhoea, 28%; headache, 21%; migraine, 14%; nasopharyngitis, 34%; nausea, 24%; bronchitis, 24%; dizziness, 10%; pyrexia, 10%; sinusitis, 31%; abdominal pain, 31%; pharyngo-laryngeal pain, 10%; chest pain, 10%; cough, 10%.

**Very common AEs (>10%):**
- infections, 68%; urinary tract infection, 24.6%; upper respiratory tract infection, 23.2%; sinusitis, 10.8%; infusion reactions; 14.3%.

**Very common AEs (>10%):**
- headache, 10.3%, 10.8%, 11.4%, 18.9%, 5.1%, 13.2%; nausea, 7.7%, 5.4%, 8.6%, 8.1%, 12.8%, 5.3%; upper respiratory tract infection, 5.1%, 0%, 2.9%, 8.1%, 15.4%, 5.3%; infusion reactions, 7.7%, 13.5%, 14.3%, 16.2%, 12.8%, 10.5%.

### ESTIMATED COST and IMPACT

#### COST

The cost of epratuzumab is not yet known.

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f SF-36 response is defined as no changes from baseline more negative than -0.8 in physical component summary (PCS) or more negative than -2.5 in any of the 8 domain scores.
**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- ✔ Reduced mortality/increased length of survival: disease activity drives organ damage; there may be a reduced mortality in the longer term due to decreased level of disease activity and organ damage.
- ✔ Reduced symptoms or disability: reduced exposure to steroids (and their long-term consequences), fewer flares of disease, and better quality of life.
- □ Other:
- □ No impact identified

**Impact on Health and Social Care Services**
- ✔ Increased use of existing services: for IV administration in clinic.
- ✔ Decreased use of existing services: should the treatment prove effective, then there could be a reduction in hospital attendance including acute admissions.
- □ 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: additional costs for IV administration in clinic.
- □ Other reduction in costs:
- □ None identified
- □ Other: uncertain unit cost compared to existing treatments.

**Other Issues**
- ✔ Clinical uncertainty or other research question identified: the issue of long-term safety.
- □ None identified

**REFERENCES**


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9 Expert personal communication.

